A study of right ventricular function during one lung anesthesia

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Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously, in its entirety or in part, submitted it at any university for a degree.

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Summary

Background to the study

OLA can give rise to certain problems:

1. A significant decrease in lung volume is reported to occur in the dependent lung during OLA in the LDP. This decrease in lung volume can result in an acute increase in opposition to RV ejection. The potential problem is that the right ventricle is a thin walled structure that can generate considerably less work than the thicker walled LV. It possesses little reserve to deal with an acute rise in afterload as may occur during acute lung injury or after lung resection. Therefore, this increase in afterload during OLA may potentially impair RV-PA coupling. Albeit this potential problem exists, the changes in RV afterload and how the right ventricle performs during OLA have not been well studied.
2. Arterial hypoxemia, due mainly to venous blood being shunted via the non-ventilated lung, may present a clinical problem during one lung ventilation.
    a. The relative resistances of the pulmonary vascular beds of the dependent ventilated and non-dependent non-ventilated lungs are an important factor governing shunting and thus arterial oxygenation during one lung anesthesia. A high non-ventilated lung PVR and low ventilated lung PVR will facilitate good arterial oxygenation during OLA. An increase in non-ventilated lung PVR is governed predominantly by hypoxic pulmonary vasoconstriction. A low opposition to pulmonary blood flow in the dependent lung is facilitated predominantly by a high alveolar oxygen tension and normal lung volume, albeit other factors also play a role in this regard.
    b. The saturation and oxygen content of mixed venous blood will contribute significantly to the arterial oxygenation in the presence of a large shunt as occurs during OLA.
        i. On the one hand, venous desaturation as a cause of hypoxemia during one lung anesthesia has not as yet been systematically addressed in the literature.
        ii. On the other hand, if RV afterload increases to such a degree that it leads poor RV performance, this may cause impairment of global circulatory efficiency and lead to mixed venous desaturation. The question that has been raised is whether inotrope infusions could improve RV and LV performance, cardiac output, and thereby the efficiency of the circulation. Increases in the efficiency of the circulation will result in an improvement in mixed venous and arterial oxygenation in the presence of a large shunt. Nonetheless, the administration of inotrope infusions in the presence of a shunt and during OLA has been reported to aggravate hypoxemia. Thus at the time of conducting the study, conflicting reports of whether increasing cardiac output and thereby mixed venous oxygenation would increase or decrease arterial oxygenation during OLA

In the light of the above, the researcher thus investigated RV afterload, RV performance and coupling to its load during OLA. The study also addressed the question whether different levels of inotrope infusion or PEEP had

beneficial or deleterious effects on RV afterload, RV performance and coupling to its load during OLA. Furthermore, if cardiac output increased during OLA secondary to the infusion of inotropes, would this improve the efficiency of the circulation, mixed venous oxygenation and thus the arterial oxygenation during OLA, or would it worsen shunt and arterial oxygenation during OLA?

Control group: OLA and the opposition to pulmonary flow

Pulmonary arterial elastance increased by between 18 to 36% during OLA and mean PAP rose by 32% after initiation of OLA This increase in mean PAP on initiation of OLA is greater than that observed by certain investigators but similar to that seen previously in patients with damaged lungs. The question arose as to why pulmonary artery pressure rises during OLA? From consideration of Ohm's law, pressure may be regarded as the product of flow and resistance (Mark, Slaughter et al. 2000). The increase in mean PAP during OLA is due to two reasons.

1. Firstly, the pressure versus flow curve is likely to be steeper during OLA. This is because pulmonary vascular recruitment and dilatation (pulmonary vascular reserve) is more limited in scope in these patients than is usual and most likely accounts for the increase in pulmonary artery pressure during OLA. The reasons for the limited pulmonary vascular reserve in the DL during OLA include:
    a. The pulmonary vascular bed of patients subjected to OLA is frequently abnormal because of its underlying pathology,
    b. During OLA in the lateral decubitus position, lung volume decreases to a greater degree than during two-lung anesthesia (Klingstedt, Hedenstierna et al. 1990).
    c. This decrease in lung volume will be further aggravated by DLT malpositions, secretions and blood, and absorption atelectasis due to the use of high concentrations of oxygen (Hedenstierna 1998; Krucylak, Naunheim et al. 1996).
    d. Excessive amounts of extrinsic or intrinsic PEEP during OLA can compress the intra-alveolar capillaries and deleteriously affect the pulmonary vascular resistance (Ducros, Moutafis et al. 1999; Inomata, Nishikawa et al. 1997; Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996).
2. Secondly, there is greater flow through this vascular bed that possesses a higher resistance.

It is noteworthy that the increase in mean PAP did not exceed a value of 25 mm Hg during OLA, even though cardiac output increased by 30%. However, in studies conducted in patients with "damaged lungs", greater increases in PA pressure (accompanied by a decrease in RVEF) have been reported to occur on PA ligation. A question arises as to why differences exist between PA clamping and OLA? The answer may well be that the observed plateau in the rise of PA pressure during OLA is as a result of progressive diversion of flow to the NDL as PA pressure rises. Support for such a suggestion comes from the observation that concomitant with increases in PA pressure during OLA, HPV is progressively inhibited and shunt fraction progressively rises. This increase in shunt fraction that has been observed to occur as PA pressure rises, reflects an increase in diversion of pulmonary blood flow to the NDL. The impact of diversion of this blood to the NDL is that it possibly acts as a safety mechanism limiting increases in PA pressure and other indices of opposition to pulmonary flow during OLA. This "blow-off effect" will protect the RV until PA clamping occurs.

Control group: OLA and RV function

The current study represented the opportunity to investigate the significance of the abovementioned increases in PA pressures and elastance on RV performance during OLA. The current study indicates that at the moderate (30%) increases in PAP that accompanied the initiation of OLA, RV performance, as judged by stroke volume, cardiac index, RVEF and RVSWI, did not deteriorate compared to the baseline awake status. In fact, cardiac output increased following surgical incision: this was probably due to sympathetic nervous system stimulation. This observation also fits in with other studies in which RV performance usually only *begins* to deteriorate when indices of opposition to RV ejection reach 200 to 250% of baseline. Furthermore, a constant preload, as indicated by unchanged central venous and pulmonary artery wedge pressures, and right ventricular end-diastolic volumes were observed throughout the study period. In other words, this increase in RV afyterlad did not cuse the RV to dilate durign OLA.

The relationship between stroke work and afterload will vary, depending on the contractile reserve of the ventricle. In this regard, it could be concluded that under the conditions operative in the current study, the RV was operating on the upslope of the RVSWI versus Ea relationship. This supports the observation that RV function is well preserved during OLA.

In conclusion, regarding the indices of opposition to pulmonary flow and RV performance during OLA, it can be concluded that:

1. Opposition to RV ejection increases. This is evidenced by a 30% rise in mean PAP and 18 to 36% increase in pulmonary arterial elastance.
2. Right ventricular performance as indicated by RVSWI, RVEF and stroke volume does not decrease during OLA compared with when the patients awake or subjected to two-lung anesthesia.
3. Furthermore, coupling between the RV and its load is well preserved during OLA. This would imply that the RV operates at close to maximal efficiency during OLA and that RV stroke work reserve is present during OLA. It is likely that the RV, which continues operating as a flow pump as it does in normal life, easily copes with the small increases in RV afterload during OLA.

Dobutamine during OLA: opposition to pulmonary flow and RV performance

The effects of dobutamine infusions on RV performance during OLA can be summarised as follows:

1. Low rates of dobutamine infusion (3 $ug.kg^{-1}.min^{-1}$) increased cardiac output, stroke volume, and RVSWI. The administration of dobutamine 3 $ug.kg^{-1}.min^{-1}$ was not accompanied by increases in RV afterload. Therefore, low infusion rates of dobutamine did benefit RV-PA coupling during OLA.
2. However, administration of higher dosages of dobutamine (5 and 7 $ug.kg^{-1}.min^{-1}$) during OLA was associated with increases in certain indices of opposition to pulmonary blood flow. For example, PA elastance, mean PA pressure, and PVR increased by 30% to 40% compared to both when the patients were awake and when both lungs were being ventilated. Furthermore, PA compliance decreased by up to 61% when dobutamine 5 and 7 $ug.kg^{-1}.min^{-1}$ were infused compared to the OLA step when dobutamine

was not administered. The increases in mean PAP and PVR are considered to be of limited clinical significance. However, the decrease in PA compliance during the infusion of the highest dosage of dobutamine is clinically significant. PA compliance represents one of the factors determining vascular impedance in the Windkessel model of the circulation. The increases in opposition to pulmonary flow and lack of progressive increase in indices of RV performance are in contrast to what is expected to occur on administration of increasing dosages of the inotrope and pulmonary vasodilator, dobutamine. The reasons for the increase in opposition to pulmonary flow include exhaustion of the pulmonary vascular reserve during OLA at the high cardiac indices of 5 to 5.5 $l.min^{-1}.m^{-2}$. This aspect overshadowed the expected pulmonary vasodilator effects of dobutamine. Moreover, it is probable that the increase in RV afterload was significant enough to prevent right ventricular performance increasing as would be expected with the administration of progressively higher dosages of inotrope.

While dobutamine was being administered during OLA, mean PAP increased to a maximum of 24.9 ± 6.2 mm Hg at a cardiac index of 5.5 ± 1.2 $l.min^{-1}.m^{-2}$. However during OLA, in the control group, mean PAP was 24.0 ± 7.7 mm Hg at the maximum cardiac index of 4.4 ± 1.1 $l.min^{-1}.m^{-2}$. This represented a relatively limited rise in PA pressure compared with administration of dobutamine alone. The most likely reason why there may have been a limited increase in mean PAP while dobutamine was being administered is that the "blow off" effect of the NDL vasculature limited the rise in PA pressure.

Oxygenation during OLA

With regard to oxygen flux, venous and arterial oxygenation during OLA in the control group, the following was observed:

1. Induction of anesthesia and the approximately 1^{O} Celsius decrease in temperature induced an approximately 40% decrease in VO_2 that continued during OLA.
2. Initiation of OLA resulted in an increase in cardiac output compared to baseline OLA and awake states.
3. The consequence was an increase in S□O_2 from 75% and P□O_2 from 5.4 kPa when the patients were awake to a P□O_2 of 9.0 ± 1.7 kPa and S□O_2 of 90.6 ± 4.7% during one-lung anesthesia.
4. During OLA, the significant increase in venous oxygenation resulted in an increase in arterial oxygenation compared to the awake state in spite of the approximately 37% shunt occuring during OLA.
5. Under conditions in the present study, dobutamine administration during OLA did not improve, but maintained the already high venous and arterial oxygenation compared with OLA alone. Therefore, the study hypothesis, that dobutamine would induce improvement in RVF and the increase in cardiac output during OLA would improve arterial oxygenation, does not hold in the current study. The hypothesis that dobutamine administration and improving cardiac output during OLA would increase arterial oxygenation was therefore rejected.

However, the rejection of the hypothesis means that the findings of the current study are in contrast to the findings of Mathru et al, and Nomoto and Kawamura. These authors demonstrated that inotrope administration resulted in an increase in arterial oxygenation. Nonetheless, the different results are not at odds with each other. In fact, these differences help to clarify the effect of increases in cardiac output on arterial oxygenation in the presence of a

significant shunt. The differences between the studies can be explained in the following way. Conditions in the *current study* resulted in a favourable DO_2/VO_2 ratio and a high starting $P\square O_2$ even before dobutamine administration was commenced. Therefore the venous saturations were on the flat part of the oxygen dissociation curve and also on the flat part of the relationship between cardiac output and arterial oxygen content originally described by Kelman, Nunn and colleagues. Further increases in cardiac output and the DO_2/VO_2 ratio would not be expected to, and did not, increase $P\square O_2$, $S\square O_2$, or $C\square O_2$. Thus, arterial oxygenation content and saturation did not change subsequent to the increase in cardiac output associated with the administration of dobutamine in the current study. In contrast, in the Mathru study, the low starting venous saturations and tensions were improved by increases in the DO_2/VO_2 ratio. As the starting venous saturation was "low," significant benefit in arterial oxygenation was obtained on increasing cardiac output in that study.

One significant concern for the clinician regarding the administration of the inotrope dobutamine during OLA is that it may increase shunt fraction (Qs/Qt) and thereby decrease arterial oxygenation during one lung ventilation. The influence of dobutamine on arterial oxygenation during OLA may theoretically be related to the balance of the following divergent effects:

1. By improving the relationship between oxygen delivery and consumption, dobutamine increases $P\square O_2$. This increase will benefit arterial oxygenation in the presence of a large shunt,
2. The above has to be weighed against possible increases in VO_2 induced by dobutamine, the consequence of which will be a decrease in $P\square O_2$. Such increases in VO_2 were not seen on administration of dobutamine in the current study,
3. An increase in PA pressure accompanying the increased cardiac output will oppose HPV and increase shunt in both the dependent and non-dependent lungs,
4. Direct inhibition of HPV by dobutamine and,
5. The influence of $P\square O_2$ on HPV (i.e. high levels of venous oxygenation will inhibit whereas low levels will potentiate HPV).

Nonetheless, in spite of the concerns (risk) of hypoxemia on administering dobutamine during OLA, dobutamine administration did not decrease PaO_2 or arterial oxygen saturation, and neither did it increase the cost of oxygenation compared to when OLA was conducted in the absence of dobutamine infusions. In addition, the findings of studies conducted by Mathru and colleagues, Nomoto and Kawamura and the current study indicate that under usual clinical conditions present during OLA in the LDP, the administration of low dosages of dobutamine do not increase shunt fraction. In fact, the beneficial effect of the increase in cardiac output on venous oxygenation resulted in an increase in arterial oxygenation in the study by Mathru and colleagues; similar mechanisms were most likely operative in the study conducted by Nomoto and Kawamura.

Therefore, there is currently no evidence that the administration of dobutamine in dosages of up to 7 $ug.kg^{-1}.min^{-1}$ increases shunt and worsens arterial oxygenation in humans subjected to OLA in the LDP. It is apparent that the vasodilatory effects of dobutamine resulting in a possible increase in shunt fraction (Qs/Qt) is therefore not the only factor to consider when studying its effects on arterial oxygenation. What is also of great relevance when

considering the effects of an inotrope on arterial oxygenation is the effect of inotropic drugs on the venous oxygen content. It is possible that Qs/Qt could be increased by the administration of inotrope. Nonetheless, if venous oxygenation is favourably affected by the administration of dobutamine, then a depressant effect on arterial oxygenation by an increase in the amount of blood passing via the shunt may be negated. If the increase in venous oxygenation is very significant, there may even be benefits in terms of arterial oxygenation, as was the case in the current study.

This approach to how the quality of the blood passing via the shunt affects arterial oxygenation shifts the emphasis on prevention and treatment of hypoxemia during OLA from the lung to the efficacy of the circulation. In other words, the emphasis is shifted from what predominantly happens to the non-ventilated lung (HPV) to primarily the efficacy of oxygen flux during OLA.

Extrinsic and intrinsic PEEP and OLA

The effects of PEEP on hemodynamics and oxygenation observed during OLA in the current study may be summarised as follows. When $PEEP_5$ was applied to the DL during OLA in the current study:

1. Neither right ventricular function, hemodynamics, oxygen flux nor arterial oxygenation was affected by the application of $PEEP_5$ compared to the step when no external PEEP was applied.
2. Significant amounts of intrinsic PEEP were present during OLA in the control group patients. The degree of intrinsic PEEP was weakly related to the degree of obstructive airways disease present on preoperative LFT's.
3. The most likely reason why $PEEP_5$ did not make a difference to oxygenation or hemodynamics was the existence of similar amounts of intrinsic PEEP during OLA. These findings confirm Myles's contention that low levels of intrinsic PEEP may have salutary effects on oxygenation during OLA.

When $PEEP_{10}$ was applied to the DL during OLA in the current study, it led to a decrease in stroke volume. This decrease is predominantly due to a decrease in preload, as PVR does not increase to levels that are known to impair RV performance. The decrease in the DO_2/VO_2 ratio that was induced by $PEEP_{10}$ predictably decreases P□O_2 and can potentially lead to impairment of arterial oxygenation. It can therefore be concluded that greater (excessive) amounts of PEEP under more unfavourable circulatory conditions than were observed in the current study, may have deleterious cardio-respiratory effects.

In summary, optimising DL volume plays an important role in determining arterial oxygenation. However, the therapeutic index for PEEP is narrow and the anesthesiologist needs to know firstly when the lung volume of the DL approaches FRC and secondly, how to avoid dynamic hyperinflation of that lung. One significant problem is that the best method of monitoring FRC during OLA is not clear at present.

Summary (Afrikaans)

Agtergrond tot die studie

Eenlongnarkose mag tot sekere probleme aanleiding gee.

'n Betekenisvolle afname in volume van die onderlong vind in die laterale decubitus posisie tydens eenlongnarkose plaas. Hierdie afname in longvolume mag egter 'n akute verhoging in regter ventrikulêre nalading tot stand bring. Die probleem is egter dat die regter ventrikel 'n dunwandige struktuur is wat potensieel baie minder werk as die dikwandige linker ventrikel kan genereer. Die regter ventrikel het min reserwe om 'n akute verhoging in nalading te weerstaan soos wat gebeur met akute longbesering of na longreseksie. Dus die verhoging in nalading wat gepaard gaan met eenlongnarkose mag die koppeling tussen die regter ventrikel en die pulmonale arterie belemmer. Alhoewel hierdie potensiële probleem bestaan, is die verandering albei in regter ventrikulêre nalading en hoe die regter ventrikel funksioneer tydens eenlongnarkose nog nie goed bestudeer nie.

1. Arteriële hipoksemie, hoofsaaklik te wyte aan die groot aftakking via die long wat nie geventileer word nie, mag kliniese probleme tydens eenlongnarkose teweegbring.
2. Die weerstand wat die pulmonale vaskulêre beddens van die geventileerde en nie-geventileerde longe bied teen bloedvloei is belangrike faktore wat aftakking en dus arteriële oksigenasie tydens eenlongnarkose beheer. 'n Hoë weerstand van die nie-geventileerde long en 'n lae weerstand van die geventileerde long se pulmonale vaskulêre beddens sal bevredigende arteriële oksigenasie tydens eenlongnarkose fasiliteer. 'n Verhoging in die pulmonale vaskulêre weerstand van die nie-geventileerde long is hoofsaaklik te wyte aan hipoksiese pulmonale vasokonstriksie. 'n Lae pulmonale vaskulêre weerstand in die geventileerde onderlong is hoofsaaklik gefasiliteer deur 'n hoë alveolêre suurstofspanning en 'n normale long volume, alhoewel alle faktore ook 'n rol in hierdie verband speel.
3. In die teenwoordigheid van die groot aftakking wat bestaan tydens eenlongnarkose, sal die saturasie en suurstof inhoud van gemeng veneuse bloed 'n betekenisvolle bydrae aan arteriële oksigenasie maak.
    a. Veneuse saturasie as 'n oorsaak van hipoksemie tydens eenlongnarkose, is nog nie sistematies in die literatuur ondersoek nie.
    b. Indien regter ventrikulêre nalading tot so 'n mate verhoog dat dit tot swak ventrikulêre uitwerp lei, mag dit 'n oorsaak wees van ontoereikendheid van die globale bloedsomloop en tot gemeng veneuse desaturasie lei. Die vraag is dus of verhoging van die kardiale omset deur inotrope ondersteuning die toereikendheid van die sirkulasie kan verbeter. Verbeterde sirkulasie toereikendheid sal tot 'n verhoging in gemeng veneuse en arteriële oksigenasie lei in die teenwoordigheid van 'n groot aftakking. Nietemin, die toediening van inotrope in die teenwoordigheid van 'n groot aftakking tydens eenlongnarkose gerapporteer om hipoksemie te vererger tydens eenlongnarkose. Dus ten tye van die uitvoer van dié studie, is daar uitdrukking gegee tot teenstrydige opinies in die literatuur oftewel verhoging in kardiale omset arteriële oksigenasie sal verbeter of versleg tydens eenlongnarkose.

In die lig van die agtergrond hierbo, het die navorser dus regter ventrikulêre nalading, regter ventrikulêre funksie en koppeling van die regter ventrikel met sy lading tydens eenlongnarkose ondersoek. Die studie het ook die vraag benader of inotroop infusies of PEEP goeie of slegte gevolge sou hê op regter ventrikulêre nalading, regter ventrikulêre funksie en koppeling van die regter ventrikel aan sy lading tydens eenlongnarkose. Sou die kardiale omset en die toereikendheid van die sirkulasie sou verbeter sekondêr tot die toediening van inotrope tydens eenlongnarkose, gemeng veneuse oksigenasie en dus arteriële oksigenasie tydens eenlongnarkose verbeter, of sou dit aftakking en arteriële oksigenasie versleg tydens eenlongnarkose?

Kontrole groep

Pulmonêre elastansie het tussen 18 en 36% verhoog en gemene pulmonale arterie druk het met 32% tydens eenlongnarkose vermeerder. Die verhoging in gemene pulmonale arterie druk met die aanvang van eenlongnarkose is groter as die waardes gesien deur sekere navorsers maar gelyk met waardes gevind in pasiënte met beskadigde longe. Die vraag ontstaan dan hoekom styg pulmonale arterie druk tydens eenlongnarkose? volgens Ohm se Wet, mag druk as die veelvoud van vloei en weerstand beskou word. Die verhoging in gemene pulmonale arterie druk tydens eenlongnarkose is daarvolgens hoofsaaklik te wyte aan twee redes.

1. Eerstens, die kurwe van druk teenoor vloei is waarskynlik styler tydens eenlongnarkose. Hierdie is omdat pulmonale vaskulêre werwing en verwyding (pulmonale vaskulêre reserwe) is meer beperk as nornaal in pasiënte met longsiekte. Hierdie is die waarskynlikste rede hoekom pulmonale arterie druk tydens eenlongnarkose verhoog. Die redes hoekom die pulmonale vaskulêre reserwe in die onderste long tydens eenlongnarkose beperk is sluit in die volgende:

1.1 Die pulmonale vaskulêre bed van pasiënte onderwerp aan eenlongnarkose mag abnormaal wees weens die onderliggende long patologie,

1.2 Tydens eenlongnarkose in die laterale decubitus posisie, is long volume in hoë mate verminder as tydens tweelongnarkose,

1.3 Die voorafgenoemde vermindering in longvolume sal verder verminder word deur wanposisies van die dubbellumenbuis, sekresies en bloed, en absorpsie atelektase.

1.4 Te hoë vlakke van PEEP, oftewel intrinsiek of ekstrensiek van oorsprong, sal die intraalveolêre vate toedruk en so die pulmonale vaskulêre weerstand verhoog.

2. Tweedens, is daar groter vloei deur hierdie vaskulêre bed wat ‘n hoër weerstand bevat.

Dit is opmerkingswaardig dat die verhoging in gemene pulmonale arterie druk ‘n waarde van 25 mmHg nie oorskry het nie tydens eenlongnarkose, alhoewel kardiale omset met 30% verhoog het. In pasiënte met beskadigde longe, het vorige studies egter bewys dat groter verhoging in PA druk gebeur tydens afbinding van die pulmonale arterie. Die vraag ontstaan dus hoekom daar verskille bestaan tussen wat gebeur tydens afbind van die pulmonale arterie en eenlongnarkose? Die antwoord mag wees dat die beperking in die styging in PA druk tydens eenlongnarkose as gevolg van ‘n progressiewe afleiding van bloedvloei na die nie-geventileerde long gebeur sodra pulmonale arterie druk styg tydens eenlongnarkose. Die implikasie van die afleiding van bloed na die nie geventileerde long is dat dit as ‘n veiligheids meganisme optree en verdere styging in pulmonale arterie druk beperk tydens eenlongnarkose. Hierdie afblaas meganisme sal die regter ventrikel beskerm tot en met PA afbind.

Kontrole groep: eenlongnarkose en regter ventrikulêre funksie

Die huidige studie bied die geleentheid om die betekenis van die voorafgenoemde verhoging in PA drukke en elastansie op regter ventrikulêre funksie tydens eenlongnarkose te ondersoek. Die huidige studie dui aan dat die 30% verhoging in pulmonale arterie druk wat met die aanvang van eenlongnarkose plaasvind, glad nie regter ventrikulêre funksie belemmer nie indien dit vergelyk word met die basislyn wakker staat. In teendeel, kardiale omset het verhoog na chirurgiese insnyding: hierdie verhoging is waarskynlik te wyte aan simpatiese senuwee stimulasie na die chirurgiese insnyding. Hierdie waarnemings pas in ook met ander studies waartydens regter ventrikulêre ejeksie alleenlik begin om af te neem indien die indekse van opposisie tot regter ventrikulêre ejeksie 200 tot 250% van basislyn bereik. Verder, die induksie van voorlading, naamlik sentrale veneuse druk, pulmonale arterie wigdruk en regter ventrikulêre einddiastoliese volumes is onveranderd tydens die huidige studie; dit beteken die ventrikel het nie gedilateer het nie tydens die verhoging in regter ventrikulêre nalading.

Die verband tussen slagwerk en nalading sal varieer, afhanklik van die kontraktiele status van die ventrikel. In hierdie opsig, kon ons aflei dat die regter ventrikel, onder omstandighede wat tydens diè studie plaasgevind het, gefunksioneer het op die stygende been van die verband tussen regter ventrikulêre slagwerk en pulmonale arterie elastansie. Hierdie waarneming ondersteun die argument in die vorige paragraaf dat die regter ventrikel funksie behoue is tydens eenlongnarkose.

Ter opsomming omtrent die indekse van opposisie tot pulmonale vloei en regter ventrikulêre funksie tydens eenlongnarkose:

1. Opposisie tot regter ventrikulêre uitwerp verhoog. Die bewys hiervoor is ’n 30% verhoging in gemene pulmonale arterie druk en ’n 36% verhoging in pulmonale arterie elastansie.
2. Ten spyte van die verhoging in weerstand teen RV uitwerping, het regter ventrikulêre funksie (soos bepaal deur regter ventrikulêre slagwerk indeks, regter ventrikulêre ejeksie fraksie en slag volume), nie verminder tydens eenlongnarkose in vergelyking met die waardes verkry wanneer die pasiënte wakker is of aan tweelongnarkose onderwerp is.
3. Ons kon ook aflei dat die koppeling tussen die regter ventrikel en sy lading goed behoue is tydens eenlongnarkose. Die implikasie hiervan is dat regter ventrikulêre slagwerk reserwe teenwoordig is tydens eenlongnarkose. Tydens eenlongnarkose funksioneer die regter ventrikel as ’n vloeipomp, net soos in normale lewe; dit beteken dat en die klein verhoging in regter ventrikulêre nalading wat ondervind word tydens eenlongnarkose maklik getolereer word.

Dobutamien tydens eenlongnarkose: opposisie tot pulmonale vloei en regter ventrikulêre funksie

Die uitwerking van dobutamien op regter ventrikulêre funksie tydens eenlongnarkose kan as volg opgesom word:

1. Lae dosisse dobutamien (3 $\mu g.kg^{-1}.min^{-1}$) verhoog kardiale omset, slagvolume en regter ventrikulêre slagwerkindeks. Die toediening van dobutamien 3 $\mu g.kg^{-1}.min^{-1}$ het nie saamgegaan met ‘n verhoging in regter ventrikulêre nalading nie. Dus, lae dosisse van dobutamien het wel die koppeling tussen die regter ventrikel en die pulmonale vaskulatuur tydens eenlongnarkose verbeter.

2. Nietemin, albei die hoër dosisse van dobutamien (5 en 7 µg.kg^{-1}.min^{-1}) tydens eenlongnarkose het verhogings in die opposisie tot pulmonale bloedvloei teweeggebring. Byvoorbeeld, PA elastansie, gemene PA druk en pulmonale vaskulêre weerstand het met 30 tot 40% verhoog in vergelyking met die waardes gekry toe die pasiënte wakker was en toe albei longe geventileer is. 'n Belangrike opmerking in hierdie opsig is dat pulmonale arterie vervormbaarheid tydens eenlongnarkose met 61% verminder het tydens albei dobutamien 5 en 7 µg.kg^{-1}.min^{-1}. Die verhogings in gemene pulmonale arterie druk en pulmonale vaskulêre weerstand is, volgens mening, nie van kliniese of statistiese betekenis nie, alhoewel die vermindering in PA vervormbaarheid tydens die dobutamien 7 µg.kg^{-1}.min^{-1} infusie wel van kliniese betekenis is. PA vervormbaarheid weerspieël *een* van die faktore wat vaskulêre impedansie in die 3-element Windkessel model van sirkulasie het. Die verhoging in opposisie tot pulmonale vloei en die afwesigheid van progressiewe verhogings in indekse van regter ventrikulêre funksie is nie wat verwag word indien die dosisse van die inotroop en pulmonale vasodilator dobutamien, progressief verhoog word. Die redes hoekom die opposisie tot pulmonale vloei verhoog tydens die toediening van dobutamien sluit in die uitwissing van die pulmonale vaskulêre reserwe tydens eenlongnarkose. Tydens die hoë kardiale indekse van 5 tot 5.5 µg.kg^{-1}.min^{-1} is die pulmonale vaskulêre reserwe uitgeput en die meganisme het die verwagte pulmonale vaskulêre vasodilatasie van dobutamien oorskadu. Bowendien is dit waarskynlik dat die verhoging in regter ventrikulêre nalading betekenisvol genoeg was om te verhoed dat regter ventrikulêre funksie progressief verhoog soos sou verwag word met die administrasie van hoër dosisse inotroop.

Die administrasie van dobutamien tydens eenlongnarkose het gemene pulmonale arterie druk verhoog tot 'n maksimum van 24,9 ± 6.2 mm Hg teen 'n kardiale indeks van 5.5 ± 1.2 l.min^{-1}.m^{2}. Nietemin is gemene pulmonale arterie druk 24.0 ± 7.7 mm Hg teen die maksimum kardiale indeks in die kontrole groep van 4.4 ± 1.1 l.min^{-1}.m^{-2} tydens eenlongnarkose in die kontrole groep. Hierdie weerspieël dus 'n relatief beperkte verhoging in pulmonale arterie druk in vergelyking met die verhoging in pulmonale arterie druk wat gebeur het tydens die administrasie van dobutamien. Die waarskynlikste rede hoekom daar 'n beperkte verhoging in pulmonale arterie druk sou gewees het tydens die infusie van dobutamien is die afblaas effek van die nie-geventileerde long wat die verhoging in PA druk beperk het.

Oksigenasie tydens eenlongnarkose

Die volgende waarnemings is gemaak in verband met suurstof vloed, veneuse en arteriële oksigenasie tydens eenlongnarkose in die kontrole groep:

1. Die kombinasie van Induksie van narkose en die 1ºC vermindering in temperatuur het saamgegaan met 'n 40% vermindering in suurstof verbruik tydens twee long narkose. Hierdie vermindering in suurstof verbruik het voortgegaan tydens eenlongnarkose.
2. Die aanvang van eenlongnarkose is geassosieerd met 'n verhoging in kardiale omset in vergelyking met albei die basislyn eenlongnarkose en wakker state.
3. Die gevolge van punte 1 en 2 hierbo is dat die gemengde veneuse suurstof saturasie vanaf 75% en die gemeng veneuse suurstof spanning vanaf 5.4 kPa (toe die pasiënte wakker was) gestyg het tydens

eenlongnarkose tot 90.6 ± 4.7% en 9 ± 1.7kPa respektiewelik.

4. Tydens eenlongnarkose het die betekenisvolle verhoging in veneuse oksigenasie veroorsaak dat daar ’n verhoging in arteriële oksigenasie was in vergelyking met wanneer die pasiënte wakker was. Hierdie styging in arteriele oksigenasie was ten spyte van die 37% aftakking wat teenwoordig was tydens eenlongnarkose.
5. Onder toestande in die huidige studie, het dobutamien tydens eenlongnarkose nog arteriële nog veneuse oksigenasie verbeter nie, maar die arteriele oksigenasie het konstant gebly. ’n Belangrike observasie wat daarmee saamgaan is dat dobutamien toediening nie met ’n *daling* in arteriële suurstof spanning geassosieer is nie. Vervolgens, die hipotese dat die verhoging in kardiale omset geassosieer met dobutamien toediening tydens eenlongnarkose ’n verhoging in arteriële oksigenasie beweeg bring, is dus verwerp.

Die verwerping van die hipotese van die deel van die studie beteken dat die bevindinge die teenoorgestelde is van die studies gepubliseer deur Mathru en sy kollegas en Nomoto en Kawamura. Hierdie outeurs het gedemonstreer dat die toediening van inotrope ’n verhoging in arteriële oksigenasie teweeg gebring het. Nietemin is die teenoorgestelde gevolgtrekkinge nie teenstrydig met mekaar nie. Inteendeel hierdie verskille help ons om die effek van ’n verhoging in kardiale omset of arteriële oksigenasie in die teenwoordigheid van ’n betekenisvolle aftakking duidelik te maak. Die verskille tussen die studies kan op die volgende manier verduidelik word. Toestande wat in die huidige studie teenwoordig was het veroorsaak dat die verband tussen suurstof lewering en verbruik baie hoog was en dat die gemeng veneuse suurstof spanning baie hoog was om mee te begin alvorens dobutamien geinfuseer is. Dus is die veneuse saturasies op die plat deel van albei die suurstof dissosiasie kurwe en ook van die verband tussen kardiale omset en arteriële suurstof inhoud oorspronklik deur Kelman, Nunn en kollegas beskryf. Verdere verhogings in kardiale omset sou dus nie verwag word, en het nie, verhogings in gemeng veneuse suurstof spanning, gemeng veneuse suurstof saturasie of gemeng veneuse suurstof inhoud teweeg gebring. Dus, arteriële suurstof inhoud en saturasie het nie verander na die verhoging in kardiale omset wat teweeg gebring is deur die toediening van dobutamien in die huidige studie. Inteendeel, in die studie deur Mathru en kollegas, is die lae aanvanklike veneuse saturasie en spanning verbeter deur verhogings in die verband tussen suurstoflewering en suurstofverbruik. Omdat die veneuse saturasie aan die begin van die Mathru studie laag was, is betekenisvolle voordeel in arterieël oksigenasie teweeg gebring deur om die kardiale omset te verhoog.

’n Groot bekommernis vir die klinikus is dat die aftakking mag verhoog met die toediening van die inotroop dobutamien tydens eenlongnarkose en, op die manier, arteriële oksigenasie mag verminder. Die invloed van dobutamien op arteriële oksigenasie tydens eenlongnarkose mag teoreties te wyte wees aan die balans van die volgende uiteenlopende faktore:

1. Deur om die verband tussen suurstof lewering en verbruik te verbeter, sal dobutamien gemeng veneuse suurstof spanning verhoog. Hierdie verhoging sal arteriële oksigenasie verbeter in die teenwoordigheid van ’n groot aftakking,
2. Die bogenoemde moet teenoor potensiële verhogings in suurstofverbruik deur dobutamien oorweeg word. Die gevolge hiervan sou potensieel ’n vermindering in gemeng veneuse suurstof spanning wees. Sulke verhogings in suurstof verbruik is nie tydens die huidige studie gesien nie,

3. 'n Verhoging in pulmonale arterie druk wat saamgaan met die verhoogde kardiale omset sal hipoksiese pulmonale vasokonstriksie teenwerk wat die aftakking in albei die geventileerde en nie geventileerde longe sal verhoog,
4. Direkte inhibisie van hipoksiese pulmonale vasokonstriksie deur dobutamien en,
5. Die invloed van gemeng veneuse suurstof spanning op hipoksiese pulmonale vasokonstriksie moet ook oorweeg word (d.i. hoe gemeng veneuse suurstof parsiele druk sal hipoksiese pulmonale vasokonstriksie inhibeer).

Nietemin, ten spyte van die bekommernisse rondom hipoksemie tydens die toediening van dobutamien tydens eenlongnarkose, het dobutamien toediening nie 'n verlaging in arteriële suurstof spanning teweeg gebring nie, en ook het dit nie die koste van oksigenasie verhoog nie. Verder, die bevindinge van studies tydens eenlongnarkose in die laterale decubitus posisie deur Mathru en sy kollegas, Nomota en Kawamura en ook die huidige studie, dui aan dat die toediening van lae dosisse van dobutamien nie toe 'n verhoging in aftakking lei nie. Inteendeel, die voordelige effekte van die verhoging in kardiale omset op veneuse saturasie het veroorsaak dat daar 'n verhoging in arteriële saturasie is in die studie deur Mathru en sy kollegas soortgelyke meganismes is waarskynlik ook van toepassing in die studie wat gedoen is deur Nomoto en Kawamura.

Dus, dwars deur die literatuur, is daar geen huidiglike bewys dat die toediening van dobutamien tot en met dosisse van 7µg.kg^{-1}.min^{-1} aftakking verhoog of arteriële oksigenasie versleg in mense onderworpe aan eenlongnarkose in die laterale decubitus posisie. Dit is duidelik dat die vasodilatoriese effekte van dobutamien wat moontlik 'n verhoging in aftakking fraksie teweeg kan bring, nie die enigste faktore is om te oorweeg wanneer die middel se invloed op arteriële oksigenasie bestudeer word nie. Dit is ook van kliniese belang om die invloed van inotrope middels op veneuse suurstof inhoud te oorweeg. Dit is moontlik dat 'n aftakking verhoog kan word deur die toediening van 'n inotroop. Nietemin, mag die negatiewe effek wat die toediening van 'n inotroop sal inhou op arteriële oksigenasie deur middel van sy verhoging in aftakking, negeer word indien veneuse oksigenasie voordelig beïnvloed is. Verder, indien die verhoging in veneuse oksigenasie wat teweeggebring word deur die toediening van inotrope baie betekenisvol is, mag die gevolg hiervan wees dat arteriële oksigenasie voordelig beïnvloed word soos die geval in die huidige studie was.

Die huidige benadering waar die kwaliteit van die bloed wat deur die aftakking vloei die arteriële oksigenasie beïnvloed, skuif die klem van voorkoming en behandeling van hipoksemie tydens eenlongnarkose van die long na die toereikendheid van die sirkulasie. Met ander woorde, die klem is geskuif van wat gebeur in die nie-geventileerde long (hipoksie pulmonale vasokonstriksie) tot primêr die toereikendheid van suurstof flux tydens eenlongnarkose.

Ekstrinsieke en intrinsieke PEEP tydens eenlongnarkose

Die invloed van PEEP op hemodinamika en oksigenasie tydens eenlongnarkose in die huidige studie mag as volg opgesom word. Toe $PEEP_5$ tydens eenlongnarkose toegedien is:

1. Nie regter ventrikulêre funksie, hemodinamika, suurstof flux nog arteriële oksigenasie is beïnvloed deur die toediening van $PEEP_5$ in vergelyking met die stap wanneer geen eksterne PEEP toegedien is nie.
2. Betekenisvolle hoeveelhede intrinsieke PEEP is teenwoordig tydens eenlongnarkose in die kontrole groep.

Die hoeveelheid intrinsieke PEEP wat teenwoordig was, is swak maar betekenisvol verwant aan die graad obstruktiewe lugwegsiekte wat teenwoordig was gemeet deur pre-operatiewe longfunksie toetse.

3. Die waarskynlikste rede hoekom $PEEP_5$ nie 'n verskil gemaak het aan oksigenasie of hemodinamika nie is die teenwoordigheid van soortgelyke hoeveelhede intrinsieke PEEP tydens eenlongnarkose. Hierdie bevinding bevestig Myle's se beweringe dat lae vlakke intrinsieke PEEP voordelige effekte op oksigenasie tydens eenlongnarkose mag hê.

$PEEP_{10}$ toediening aan die onderlong tydens eenlongnarkose in die huidige studie het tot 'n vermindering in slagvolume gelei. Hierdie vermindering is primêr veroorsaak deur 'n vermindering in voorlading en nie die gevolg van 'n verhoging in pulmonale vaskulêre weerstand nie. Die gevolgtrekking is gemaak omdat regerventrikulere enddiastoliese volume verlaag het maar pulmonale vaskulêre weerstand het nie verhoog tot vlakke wat bekend is om regter ventrikulêre funksie te belemmer nie. Die vermindering in die verhouding tussen suurstof lewering en suurstof verbruik wat geïnduseer is deur $PEEP_{10}$ het (voorspelbaar) gemeng veneuse suurstof spanning verminder en kon potensieël gelei het tot belemmering in arteriële oksigenasie. Indien minder voordelige sirkulatoriese toestande geheers het tydens die huidige studie, sou groter (oorbodige) hoeveelhede PEEP slegter kardiorespiratoriese gevolge tot gevolg gehad het.

Ter opsomming, optimalisering van die volume van die onderlong tydens eenlongnarkose speel 'n belangrike rol in die bepaling van arteriële oksigenasie. Nietemin, die terapeutiese indeks vir PEEP is nou en die narkotiseur het die behoefte om te weet wanneer die volume van die onderlong optimaal is. In die opsig, is 'n betekenisvolle probleem tydens eenlongnarkose dat meting van funksionele residuele kapasiteit nie huidiglik maklik is nie.

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- Buying, selling and packing and unpacking houses
- The conception of Carol and my first child
- The illness of my father
- The birth of Talia Hannah Margaret
- The passing of my father
- The conception of our second child
- Amongst the above, a GCP project, busy clinical programme, many lectures, 2 operations and 2 legal battles were conducted

We have been granted grace to heal. I trust this work will contribute to this.

Nonetheless, grace ultimately belongs to Hashem:

בּרוּך אתה יי אלהנוּ מלך העוֹלם אשׁר יצר את האדם בּחכמה וּבּרא בּוֹ נקבים נקבים חלוּלים חלוּלים. גדלוּ וידוּע אחד מהם אוֹ יסתם אחד מהם אי אפשׁר להתך ים ולעמוֹד לפניךָ. בּרוּך אתה יי רוֹפא כל בּשׂר וּמפליא לעשׂוֹת. לפני כסא כבוֹדךָ שׁאם יפתח אחד מהם אוֹ יפתח

Blessed are you, the holy force ruling the universe, for understanding and guiding our development, including that of our many organs and passages. While being accountable before you, we become aware of our frailty and mortality; according to your prerogative, if even one of our organs or passages rupture or become obstructed, we cannot continue. Blessed are you, the holy force guiding over the universe, for wondrously functioning as our physician.

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1. Literature Review

1.1 The relevance of the right ventricle (RV)

Relatively little information exists concerning the physiology and pathophysiology of the normal right ventricle, as compared to the considerable knowledge regarding left ventricular function. The reasons for the emphasis placed on the left ventricle are:

- The thicker walled left ventricle generates considerably more hydraulic power than the relatively thin walled right ventricle. This thicker walled chamber dominates our physiological considerations of normal and abnormal cardiac function (Piene 1986; Ferlinz 1982). The current prevalence of ischemic heart disease and systemic hypertension predominantly express their deleterious effects on the left ventricle. Thus, the perception exists that the LV is the chamber that presents an immediate threat to human life if it fails.
- Studies of right ventricular function initiated as long ago as the 1940's left the impression that the right ventricle, under normal physiological conditions, is an unimportant and dispensable "flow pump" (Rigolin, Robiolio et al. 1995; Sunagawa, Maughan et al. 1983; Ferlinz 1982; Sade and Castaneda 1975; Donald and Essex 1954; Kagan 1952).

The question then arises whether the RV is of importance in human physiology or is it a dispensable pump? The issue may be examined using two approaches. On the one hand, the validity of the concept of the 'dispensable' right ventricle needs to be examined. This will be approached by examining the history of the concept of the "dispensable RV". On the other hand, evidence needs to be lead of situations when the right, rather than the left ventricle, is the significant factor in limiting survival of the organism.

1.2 The right ventricle, dispensable or essential pumping chamber?

1.2.1 The concept of the dispensable right ventricle

Isaac Starr and co-workers conducted a study with the stated aim of to demonstrating the fallacy of the concept of univentricular failure (Bakos 1950). At the time, a debate was being conducted whether a rise in central venous pressure could be an indication of left, rather than right, ventricular failure (Bakos 1950; Starr, Jeffers et al. 1943). An approach to solve this problem was developed whereby the free wall of the right ventricle was inactivated and the physiological consequences thereof were then studied. The free walls of canine right ventricles were inactivated by cauterising them with a soldering iron, but without perforating the ventricle. An alternative model also used by these authors was to inactivate the RV free wall by selectively ligating the coronary arteries that supply it. The left ventricle was spared. An insignificant rise of only one to two cm H_2O in central venous pressure was observed after either method of RV free wall inactivation was applied. Starr and his colleagues therefore observed that the RV was not essential for maintenance of circulatory homeostasis in their experimental dog models. Incidentally, their conclusions were that the rise in central venous pressure seen in cardiac disease is not necessarily associated with selective failure of the right ventricle.

Starr's original article prompted the conduct of similar experiments that studied aspects of right ventricular function

(Sunagawa, Maughan et al. 1983; Donald and Essex 1954; Kagan 1952; Bakos 1950). Bakos subsequently demonstrated that right ventricular stroke volume was maintained and pulmonary artery pressures were unchanged despite the damage sustained on RV free wall inactivation (Bakos 1950). Furthermore, both Kagan (Kagan 1952), and Donald and Essex (Donald and Essex 1954) suggested that such damaged right ventricles sustained their performance even in the face of pulmonary artery constriction. The source of power for the maintenance of the circulation after the destruction of the right ventricular free wall was at the time never satisfactorily resolved (Sunagawa, Maughan et al. 1983). Proposed explanations have included:

1. Residual deeper undamaged muscle fibres of the right ventricular free wall (Sunagawa, Maughan et al. 1983; Bakos 1950);
2. Mechanical transmission of left ventricular energy by encircling bands of muscle (Kagan 1952). However, the absence of visible contraction of the right ventricular free wall in the aforementioned experiments does not support this hypothesis (Sunagawa, Maughan et al. 1983) or,
3. Contributions from the interventricular septum (Sunagawa, Maughan et al. 1983; Ferlinz 1982; Donald and Essex 1954; Kagan 1952).

These experiments lead to the following consensus. The right ventricle is predominantly a passive conduit and its function as a pump is largely superfluous (Rittenhouse, Berger et al. 1978). The next logical step was to attempt exclusion of the right ventricle from the circulation (Sade and Castaneda 1975). The desire to exclude the right ventricle from pumping blood through the pulmonary circulation was prompted in an attempt to help patients with congenital obstructive and shunt lesions of the right side of the heart (Lake 1999; Sade and Castaneda 1975). Sade and Castaneda (Sade and Castaneda 1975) reviewed the historical development of attempts to bypass the RV in an article with the unfortunate title of "*The Dispensable Right Ventricle*" (Ferlinz 1982). During the first attempts in 1949 at performing these bypass procedures, dogs did not survive acute exclusion of the right ventricle from the circulation when the venous return was shunted directly into the pulmonary artery. (It must be noted that this observation contradicts the conclusion that the RV is a dispensable chamber.) Following these initial futile attempts to bypass the RV, a novel approach was described in 1954. This involved the performance of a prior procedure during which tricuspid stenosis was created. The presence of tricuspid stenosis induced right atrial hypertrophy (Sade and Castaneda 1975; Nuland, Glenn et al. 1958). What is noteworthy is the animals *did* subsequently survive if the hypertrophied right atrium was anastomosed to the pulmonary artery and acted as the pumping chamber (Sade and Castaneda 1975). Glenn, in 1954, achieved partial RV exclusion by performing a superior vena cava to right pulmonary artery anastomosis (Sade and Castaneda 1975; Fontan and Baudet 1971; Nuland, Glenn et al. 1958; Patino, Glenn et al. 1956). Robisek and his colleagues eventually achieved success in 1956 in totally bypassing the right heart. They did this by anastomosing the inferior vena cava to the left atrium, in addition to performing a Glenn shunt (Bergel and Milnor 1965; Sade and Castaneda 1975; Nuland, Glenn et al. 1958). Only in 1969, did Fontan and Baudet perform a total cavo-pulmonary shunt in humans (Robicsek 1992; Gale, Danielson et al. 1980; Fontan and Baudet 1971).

The statement made by Sade and Casteneda that the right-sided pumping chamber is dispensable, is not unequivocally upheld after close scrutiny of the literature. The reasons for casting doubt on the "dispensability" of the RV include:

1. In most of the studies, the animals used had normal pulmonary vasculature. It is well described that the right ventricle becomes progressively more important as pulmonary vascular resistance rises (Sunagawa, Maughan et al. 1983; Kagan 1952). Furthermore, criteria for a successful outcome when doing procedures that exclude the right heart heavily emphasize the presence of a low pulmonary vascular resistance (Morel, Costabella et al. 1990; Sade and Castaneda 1975).
2. Guiha et al, prompted by their experience with 6 cases of inferior infarction complicated by right ventricular myocardial infarction and failure, repeated Starr's original experiment (Sunagawa, Maughan et al. 1983). Unlike the other investigators before them (Donald and Essex 1954; Kagan 1952; Bakos 1950; Starr, Jeffers et al. 1943), their experimental protocol also included measurement of aortic flow and the response of the ventricles to volume loading. Right ventricular end-diastolic pressure did not increase significantly from before (2.6 mmHg) to after (5 mmHg) cauterisation. Furthermore, pulmonary artery pressures were unchanged. This is in keeping with the results of previous experiments. However, these normal pressures belied considerable impairment of ventricular function as evidenced by a 20% decrease in aortic blood flow and a marked shift to the right in the right ventricular function curve (Sunagawa, Maughan et al. 1983). After destruction of the right ventricle, the left ventricular (LV) function curves did not change significantly but left ventricular filling decreased (Sunagawa, Maughan et al. 1983). This observation is supported if Starr's original work is closely examined. It is evident that decreases in mean arterial blood pressure (from 130 to 70 mmHg) did occur on cautery of the RV free wall (Starr, Jeffers et al. 1943). This emphasises the role that ventricular-ventricular systolic interaction has in determining cardiac performance.
3. Contributions from the left side of the circulation may support the failing right ventricle (Rittenhouse, Berger et al. 1978; Raines, LeWinter et al. 1976). However, when an increase in stroke work is needed (due to an increase in cardiac output as during exercise, or increase in right ventricular ejection pressure), this mechanism may be inadequate to sustain an adequate circulation (Rittenhouse, Berger et al. 1978).
4. Destruction of the right ventricular free wall was always performed in animal models in which the pericardium had been opened (Sunagawa, Maughan et al. 1983; Donald and Essex 1954; Kagan 1952; Bakos 1950; Starr, Jeffers et al. 1943). An intact pericardium limits the great compliance and distensibility of the right ventricle, and plays a significant role in ventricular interdependence. Left ventricular function may have been more compromised and the rise in right ventricular end-diastolic pressure greater, if the integrity of the pericardium had been preserved (Milnor 1982c).
5. The majority of the studies relied on measurement of right ventricular end-diastolic pressure (RVEDP) and did not measure end-diastolic volume (RVEDV) of the right ventricle. The relationship between end-diastolic pressure and end-diastolic volume of the compliant right ventricle has frequently been reported to be poor (Diebel, Wilson et al. 1992; Dhainaut and Squara 1992; Martyn, Snider et al. 1981).

1.2.2 Right ventricular function critical to survival

In contrast to the concept of the dispensable right ventricle, we will briefly examine situations where the right ventricle may be the ventricle that determines survival by being the limiting factor in the circulation (Nyhan 2001; Nyhan 2001).

1.2.2.1 Respiratory Failure

In 1977, Zapol and Snider first described that pulmonary hypertension occurs during acute lung injury (ALI) or adult

respiratory distress syndrome (ARDS), in spite of correction of arterial hypoxemia (Zapol and Snider 1977). Both they and others have observed that the ability of the right ventricle to sustain an acutely imposed workload was an important factor in the ultimate survival or death of the patient with ALI (Brunet, Dhainaut et al. 1988; Zapol and Snider 1977). Survival from ARDS has been associated with a lower pulmonary vascular resistance (PVR) (Shoemaker and Kram 1998; Sturm, Lewis, Jr. et al. 1979) and improvement in right ventricular function with time (Eddy, Rice et al. 1988).

1.2.2.2 Sepsis

Clowes and colleagues, in a remarkable and prophetic article published in 1969, accurately documented that the circulatory insufficiency and inadequate delivery of oxygen to the tissues seen in sepsis was primarily caused by right ventricular failure (Clowes, Jr., Farrington et al. 1970). This has been validated and expanded upon by others:

1. Thrombi that form in the pulmonary vasculature in patients with sepsis lead to increases in PVR, pulmonary hypertension, increased right ventricular stroke work and ultimately RV failure (Hoffman, Greenfield et al. 1983; Guntheroth, Kawabori et al. 1978). Survivors demonstrated increases in PVR (152 +/- 36%) and cardiac index (4.4 litres.min^{-1}.m^{-2}) that remained constant over time. However, in non-survivors, PVR increased progressively to approximately 600% of control and cardiac index decreased to 2.2 litres.min^{-1}.m^{-2} before death (Sibbald and Driedger 1983; Clowes, Jr., Farrington et al. 1970).

	Central venous pressure (cm H_2O)		
	Onset	Maximal response	Convalescence / Pre-mortem
Survivors	4 ± 3	9 ± 4	5 ± 2
Non-survivors	4 ± 4	12 ± 5	19 ± 5

Table 1.2.2.2.1 CVP values of patients with sepsis as reported by Clowes and colleagues, 1970. Data presented as mean and standard deviation.

2. The right, rather than the left ventricle, may be the limiting factor determining survival in sepsis (Hoffman, Greenfield et al. 1983). Right ventricular dysfunction in sepsis has been reported to be worse and more consistently present than left ventricular dysfunction (Mitsuo, Shimazaki et al. 1992; Parker, McCarthy et al. 1990; Reuse, Frank et al. 1988; Hoffman, Greenfield et al. 1983). Circulating factors in sepsis induce biventricular myocardial depression and systemic vasodilatation (Grocott-Mason and Shah 1998; Parker, McCarthy et al. 1990; Reuse, Frank et al. 1988). The resultant arterial hypotension adversely affects perfusion of the stressed right ventricle, which contributes to right ventricular dysfunction (Reuse, Frank et al. 1988; Hoffman, Greenfield et al. 1983). Other investigators have demonstrated right ventricular dilatation (defined as an increased right ventricular end-diastolic volume normalized for body surface area) in sepsis (Mitsuo, Shimazaki et al. 1992; Dhainaut, Lanore et al. 1988; Hoffman, Greenfield et al. 1983). The resultant leftward shift of the interventricular septum would, at least in part, explain the observed

decrease in compliance of the *left* ventricle seen in sepsis (Mitsuo, Shimazaki et al. 1992; Dhainaut, Lanore et al. 1988). Furthermore, many of these patients develop adult respiratory distress syndrome (ARDS), which has significant implications for RV-PA interaction.

3. The prognostic value of right ventricular function in sepsis has been documented whereas no relationship between survival and left ventricular function was seen (Hoffman, Greenfield et al. 1983). The initial right ventricular ejection fraction (RVEF) is significantly higher in survivors of sepsis (Reuse, Frank et al. 1988). Furthermore, an improvement of the RVEF over time is an indicator of survival (Hoffman, Greenfield et al. 1983). However, these factors may simply be related to the severity of the sepsis and the accompanying severe myocardial depression (Reuse, Frank et al. 1988).

1.2.2.3 Right ventricular performance and pulmonary resection

Resection of lung tissue results in the removal of both lung parenchyma and a portion of the pulmonary vasculature. Should the remaining vascular bed not allow further recruitment and dilation in response to an increase in cardiac output, PA pressure will then rise (Lewis, Bastanfar et al. 1994). Depending on firstly the degree of rise in pulmonary artery pressure for a particular rise in the cardiac output and secondly the right ventricular reserve of the RV, the patient may either tolerate the new physiological status or exhibit various degrees of right ventricular dysfunction (Coetzee 2000; Bolliger, Jordan et al. 1995). This dysfunction may span a spectrum from, on the one hand, allowing a sedentary lifestyle to, on the other hand, the development of acute right ventricular failure and death (Okada, Ota et al. 1994; Gass and Olsen 1986). The amount of pulmonary vascular reserve and right ventricular function needs to be considered before pulmonary resection is undertaken (Okada, Ishii et al. 1996; Gass and Olsen 1986).

Pneumonectomy after hemorrhagic shock carries a dismal prognosis in humans and animal models alike (Cryer, Mavroudis et al. 1990). The reasons appear to be the development of acute pulmonary hypertension within 4 hours of the insult. Pulmonary vascular resistance increase was shown to exceed 500% of baseline 4 hours after pneumonectomy. This was followed by acute RV dysfunction and death of the organism. Causes of this marked increase in PVR include the release of thromboxane and pulmonary leucostasis (Cryer, Mavroudis et al. 1990). Whatever the mechanisms suggested, it is most likely that these animals developed ARDS after this insult.

1.2.2.4 Right ventricular infarction

Cohn and colleagues (Cohn, Guiha et al. 1974) were the first to report on right ventricular failure complicating left ventricular infarction. They suggested that the infarcted right ventricle could not generate enough pressure to fill the ischemic and non-compliant left ventricle. In other words, when the ischemic right ventricle is faced with an acute rise in PA pressure with which it cannot cope, RV dysfunction becomes evident. However, isolated RV infarction (without dysryhmias or LV extension) is usually a hemodynamically silent event.

1.2.2.5 Right ventricular dysfunction after cardiopulmonary bypass

Acute right ventricular dysfunction (Stein, Breisblatt et al. 1990) can be a cause of morbidity and mortality after cardiac surgery. Causes for this include heparin-protamine reactions resulting in acute pulmonary hypertension and poorer protection of the RV especially by retrograde cardioplegia (Morel, Costabella et al. 1990).

1.2.2.6 Pulmonary embolism

Acute pulmonary embolism, be the cause thrombi, air, carbon dioxide, or amniotic fluid may impose a strain on the right ventricle to a greater degree than that imposed by simple physical obstruction of the pulmonary vascular bed. This is the result of pulmonary vasoconstriction induced by the release of a number of vasoactive mediators (Goldhaber 1997; Moser 1990). It is well described that such an acute rise in RV afterload is not well tolerated by the thin walled right ventricle and the resultant right ventricular dysfunction is the primary reason for the ensuing circulatory instability (Goldhaber 1997; Moser 1990).

1.2.2.7 Lung and heart transplantation

Right ventricular dysfunction may present problems after heart transplantation (Firestone 1991). A pre-existing pulmonary vascular resistance of more than 480 to 640 dynes.sec.cm^{-5} is regarded as a contraindication to cardiac transplantation (Reichart, Reichenspurner et al. 1987).

Right ventricular failure is often a problem during and early after, bilateral sequential lung transplantation and may be the cause of death (Myles, Weeks et al. 1997; Kendall, Bittner et al. 1997; Kirshbom, Tapson et al. 1996; Van Trigt, Bittner et al. 1995).

1.2.2.8 Dynamic hyperinflation

Dynamic hyperinflation is a clinically significant problem during one lung anesthesia (OLA) in patients with acute asthma, chronic obstructive pulmonary disease (COPD) and intrinsic positive end-expiratory pressure (PEEPi) or with malpositions and obstructions of a double lumen tube (DLT) (Levy, Kitch et al. 1998; Conacher 1998; Inomata, Nishikawa et al. 1997). This will raise intra-alveolar pressure and PVR and eventually produce signs of right ventricular dysfunction, systemic hypotension and even cardiac arrest (Conacher 1998; Myles, Weeks et al. 1997; Conacher 1997; Naunheim and Ferguson 1996; Mercer 1995; Myles, Madder et al. 1995; Jardin, Dubourg et al. 1987).

Based on the above, it can justifiably be concluded that the right ventricle is not only a vital part of the cardiovascular system but may on occasion represent the physiologically dominant ventricle.

Contributions from the left side of the circulation may support the failing right ventricle (Rittenhouse, Berger et al. 1978; Raines, LeWinter et al. 1976). However, when an increase in stroke work is needed (due to an increase in cardiac output as during exercise, or increase in right ventricular pressure), this mechanism may be inadequate to sustain an adequate circulation (Rittenhouse, Berger et al. 1978).

1.3 Applied anatomy and physiology of the right ventricle

Both right ventricular function and anatomy differ from that of its counterpart, the left ventricle. However, the two ventricles are in intimate contact and their function and anatomy influence each other. The anatomy of the right ventricle in relationship to its physiology will be addressed.

The systolic function of the RV has similar determinants to those of the left ventricle namely preload, afterload and

contractility (Calvin, Jr. 1991; Sibbald and Driedger 1983). The extent that the left and right ventricles differ in utilizing any one or a combination of these factors in their adaptive response to stress is unclear (Weber, Janicki et al. 1983; Sibbald, Paterson et al. 1978). The right ventricle is exquisitely sensitive to afterload and this concept will be emphasized (Hurford and Zapol 1988).

1.3.1 Anatomy

In utero the right ventricle is the dominant ventricle. It ejects 66% of the cardiac output and shares a similar preload and afterload with the left ventricle (Wiedemann and Matthay 1997; Hines and Barash 1993; Weber, Janicki et al. 1983). During the first three months of life, the RV has the greater mass and continues to be the dominant ventricle.

On the one hand, pulmonary vascular resistance decreases and attains adult levels 2 weeks after birth (Hines and Barash 1993). Thereafter, even with a 200 to 300% increase in cardiac output during exercise, PA pressures do not rise much (Rigolin, Robiolio et al. 1995). On the other hand, after birth the LV is faced with a significantly higher vascular resistance than it experienced in utero. The different load and wall stresses faced by the two ventricles in adult life causes remodelling to occur (Weber, Janicki et al. 1983). Wall thickness and muscle mass of the left ventricle exceeds that of the RV after the 24th month of life (Hennebry and Gerstenblith 2001).

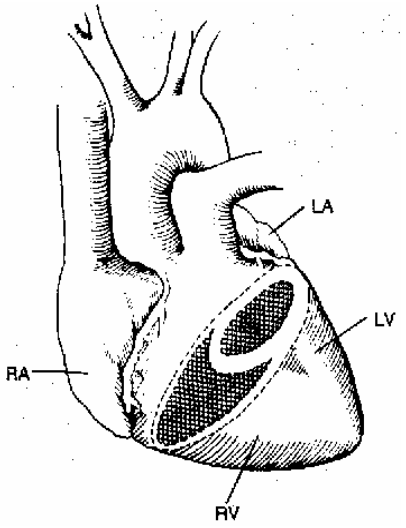


Figure 1.3.1.1. The anatomical relationship of the right ventricle showing the conical shape of the left ventricle, and half moon shape of the larger anterior right ventricle. Wiedemann et al, 1997

Normal adult right ventricular weight is less than 65 grams in men and 50 grams in women. The relationship of LV including septal, to RV mass ranges between 2.3 and 3.3 to 1 (Wiedemann and Matthay 1997). Normal right ventricular free wall thickness is less than or equal to 5 mm. Therefore the adult RV is significantly thinner than the LV wall that is normally less than 9 to 11 mm in thickness (Hennebry and Gerstenblith 2001; Wiedemann and Matthay 1997). The implications of being the "lightweight" ventricle with the thinner wall is that right ventricular compliance is much greater than that of the left ventricle, and the reserve to do work and generate pressure is much less than that of the LV (Rigolin, Robiolio et al. 1995).

The RV lies anteromedial in relation to the LV. It therefore forms most of the anterior surface of the heart (Figure 1.3.1.1) (Rigolin, Robiolio et al. 1995; Hines and Barash 1993; Milnor 1982c). The normal RV viewed in cross section is crescent shaped (Wiedemann and Matthay 1997; Dodson, Nathan et al. 1997; Hines and Barash 1993; Calvin, Jr. 1991). Albeit this issue has elicited much discussion, the shape of the right ventricle has been described as a pyramid with a triangular base (Hennebry and Gerstenblith 2001; Rigolin, Robiolio et al. 1995).

The muscle fascicles of the heart envelop both ventricles in one continuous sweep (Figure 1.3.1.2) (Thomas 1957; Bakos 1950). Because of this arrangement, the interventricular septum is, during normal physiological states, considered as an anatomic and functional as part of the left ventricle (Hennebry and Gerstenblith 2001; Stoltzfus

1997; Dodson, Nathan et al. 1997; Rigolin, Robiolio et al. 1995).

The RV is embryologically and functionally divided into antero-superior **outflow** and postero-inferior **inflow** regions that are separated by the crista supraventricularis (Dodson, Nathan et al. 1997; Rigolin, Robiolio et al. 1995; Calvin, Jr. 1991; Hurford and Zapol 1988; Armour, Pace et al. 1970). The inflow region begins to contract 25 to 50 milliseconds before the outflow region: a peristaltic type of contraction therefore exists in the RV (Hennebry and Gerstenblith 2001; Dodson, Nathan et al. 1997; Armour, Pace et al. 1970). This sequence of contraction may be a result of the larger number of Purkinje fibres present in the inflow region and the paucity of thereof in the outflow tract. The outflow tract also has greater contractile reserve partly due to a better (parallel) arrangement of the muscle fibres, and partly because contraction lasts longer than in the inflow tract (Dodson, Nathan et al. 1997; Armour, Pace et al. 1970). Sympathetic nervous system stimulation has been shown to produce a pressure gradient of up to 40 mmHg between the inflow and outflow regions of the RV (Piene 1986; Raines, LeWinter et al. 1976; Pace, Keefe et al. 1969). On the one hand, this gradient has been suggested to protect the pulmonary vasculature from high pressures developed by the inflow region. Piene, on the other hand, has suggested that such stricture formation may be a disadvantage and result in considerable energy loss during right ventricular ejection (Piene 1986).

1.3.2 Right ventricular contraction

The LV contracts by coaxial (radial) shortening of its fibres. This action results in the interventricular septum being pulled leftward (Figure 1.3.2.1) (Rigolin, Robiolio et al. 1995). In contradistinction to the simple radial shortening of the fibres in the LV, right ventricular ejection involves the co-ordinated contraction of three distinct components (Figure 1.3.2.1) (Hennebry and Gerstenblith 2001; Rigolin, Robiolio et al. 1995; Hines and Barash 1993). These three components comprise the RV free wall, the septum and the conus.

1. The **spiral muscles** initiate right ventricular contraction (Figure 1.3.1.2). This results in shortening of the fibres of the free wall of the right ventricle. This shortening causes RV **free wall translation** toward the septum (Figure 1.3.2.1). This action comprises the major part of RV contraction. RV free wall movement therefore acts as a bellows to expel blood from the right ventricle (Piene 1986). The action of the **crista supraventricularis**, which is also contracting at this time, is to link the RV free wall to the LV (Hennebry and Gerstenblith 2001).
2. At the time of maximal RV free wall contraction, the septum is only beginning to contract (Hennebry and Gerstenblith 2001). The decrease in RV free wall surface area is assisted by the septal contraction in 2 ways. Firstly, septal stiffening prevents it bulging into the LV when the RV contracts. Secondly, traction is applied by the septum at the point of its attachment of the RV. RV free wall contraction is aided by this pulling action of septal contraction (Rigolin, Robiolio et al. 1995). The conus (outflow region) is the last part of the RV to initiate contraction.

RV ejection into the PA has been shown to continue even after the delayed contraction of the outflow tract has ceased and after the end-systolic pressure (Pes) has been reached. This is unlike that of the LV ejection into the aorta, where ejection definitely ceases by the time Pes occurs (Hennebry and Gerstenblith 2001).

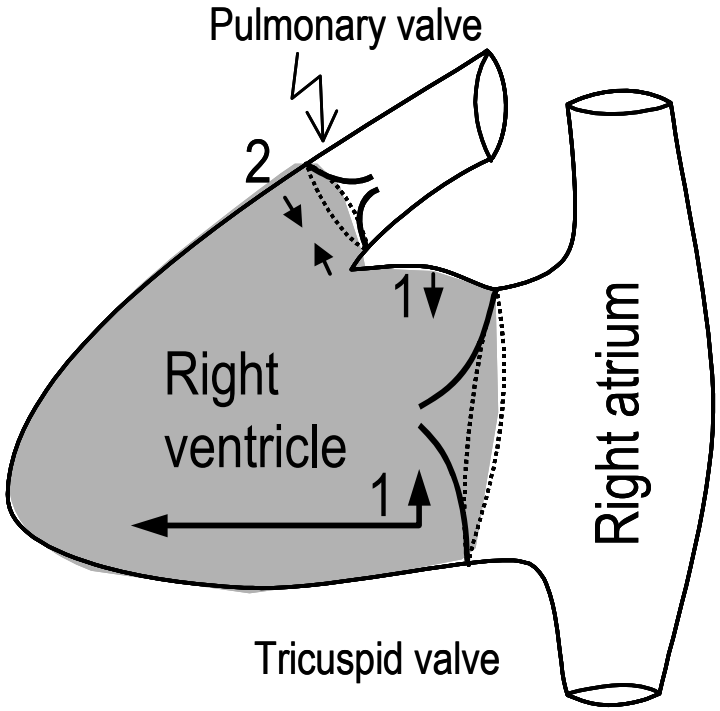


Figure 1.3.2.1.

A diagrammatic representation of the sequence of RV contraction. The RV contraction first begins at the inflow area and the RV free wall (arrows marked with "1"). Thereafter the outflow tract (conus, or area marked with a "2") contracts.

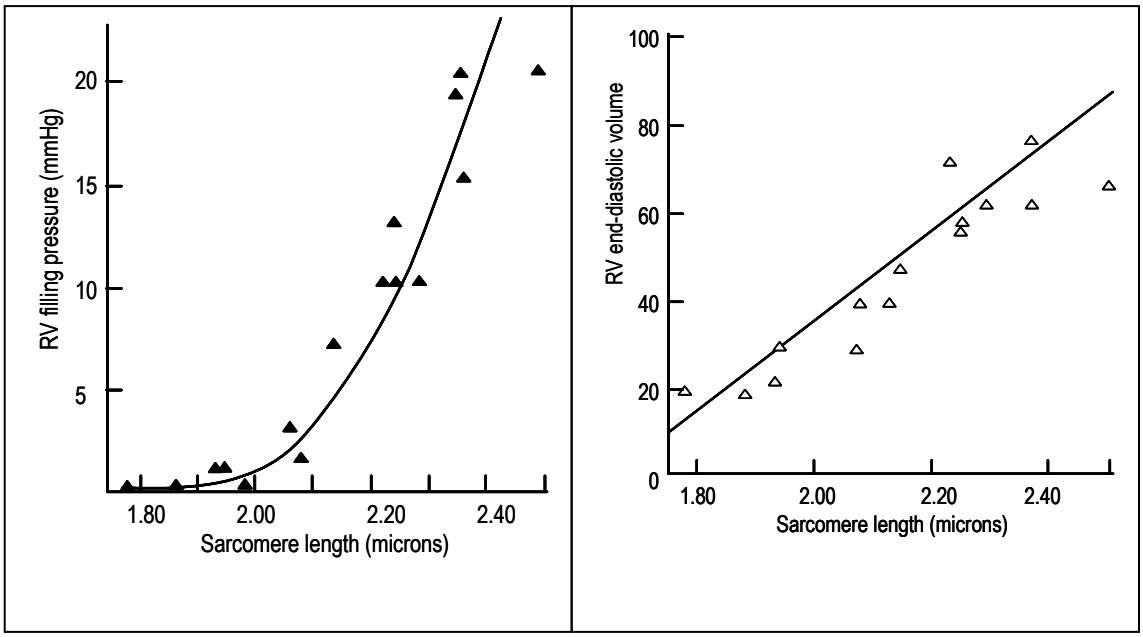
Redrawn and adapted from Hennebry and Gerstenblith, 2001

It has also been suggested that RV ejection is a dual process. The first part is unequivocally a result of RV muscle contraction. The second part is suggested to be due to the momentum of the blood that is being ejected into the low resistance pulmonary vasculature (Hennebry and Gerstenblith 2001). However, this second phase of the RV ejection process is more likely a result of systolic ventricular interaction (Santamore, Lynch et al. 1976a).

1.3.3 Preload

1.3.3.1 Isolated muscle

In an isolated muscle preparation, preload is the load imposed on the muscle before contraction and is obtained by stretching the muscle to a certain length (Braunwald, Ross, Jr. et al. 1967). (See Figure 1.4.1 and the accompanying discussion). The length that the muscle is stretched to at the end of diastole determines the force generated during the subsequent contraction. The physiological basis of this is that as muscle length increases, greater actin-myosin overlap occurs resulting in optimal crossbridge formation with optimal tension generation (Leyton, Spotnitz et al. 1971) This optimal end-diastolic muscle length corresponds to a sarcomere length of 2.2 microns for left ventricular papillary muscle (Figures 1.3.3.1.1a, b and c) (Thys and Dauchot 1998; Braunwald, Ross, Jr. et al. 1967). This corresponds closely to studies on sarcomere length done on the intact dog right ventricle. This is an important observation as the RV has a larger end-diastolic volume than that of its counterpart (Leyton, Spotnitz et al. 1971).



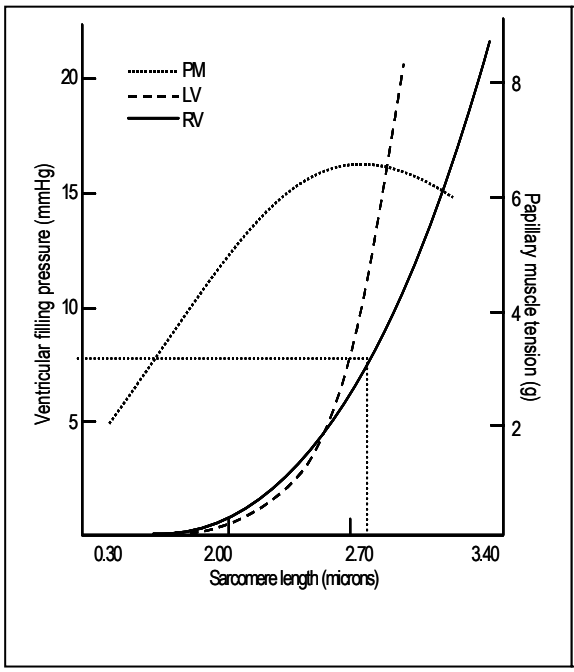


Figure 1.3.3.1.1a. Top left hand figure: RVEDP versus sarcomere length for the canine RV.

Figure 1.3.3.1.1b Top right hand figure: RVEDV versus sarcomere length for the canine RV. Adapted from Leyton, 1971.

Figure 1.3.3.1.1c. Left hand figure: Left ventricular filling pressure and tension versus sarcomere length in intact dog ventricle. Superimposed on these curves, the tension developed by isolated cat papillary muscles is plotted as a function of sarcomere length. The apex of the length tension curve for papillary muscle corresponds to a filling pressure in the canine LV of 12 mmHg and in the RV of 7 mmHg. PM = Papillary muscle. RV = Right ventricle. LV = Left ventricle.

Adapted from Braunwald et al, 1967 and. Leyton et al, 1971.

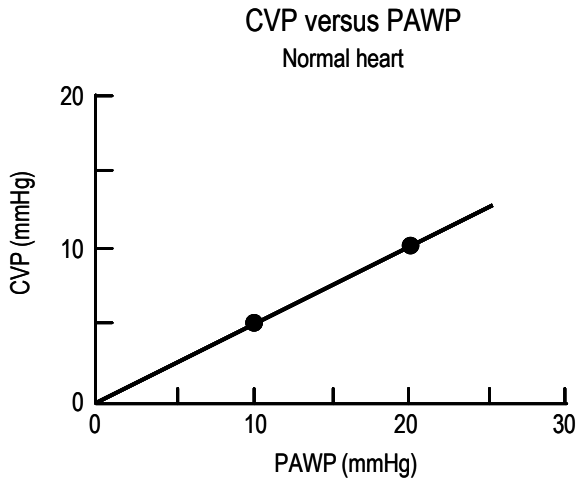


Figure 1.3.3.1.2. Simultaneous measurements of central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP) made during preload changes in a normal hearts. Adapted from Benumof, 1998.

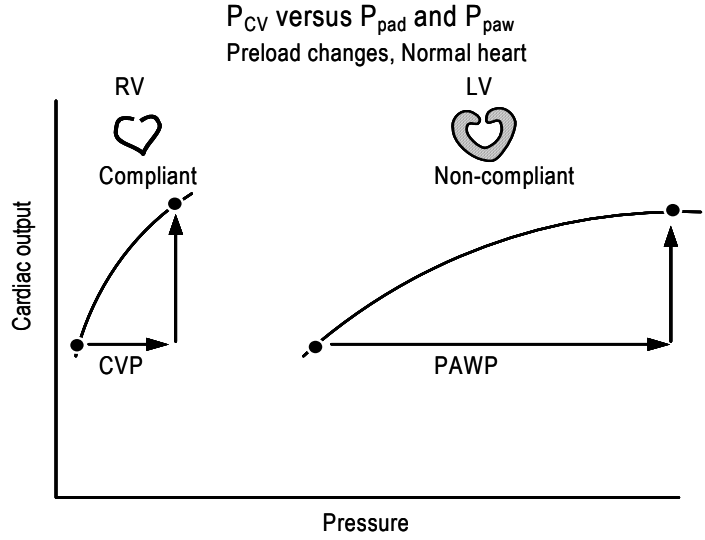


Figure 1.3.3.1.3. The relationship between central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP) is normally based on the difference in compliance between the thick walled and relatively less compliant LV and the thinner walled RV. Therefore, a small rise in CVP is accomplished by a much larger rise in pulmonary artery wedge pressure for a given rise in increase in cardiac output. Adapted from

1.3.3.2 Intact ventricle

For the intact left and right ventricles, preload is best defined as end-diastolic wall stress (the force per cm^2) distending the ventricle at the end of diastole (Hennebry and Gerstenblith 2001; Jacobsohn, Chorn et al. 1997). The determinants of diastolic wall stress are end-diastolic volume, end-diastolic pressure and wall thickness. To be able to apply this to an intact ventricle, ventricular volumes may be substituted for wall stress, as both right and left ventricular volumes have been shown to correlate well with sarcomere length (Thys and Dauchot 1998; Leyton, Spotnitz et al. 1971).

Leyton and colleagues studied the relationship of sarcomere length to right ventricular end-diastolic pressure and volume in the intact dog right ventricle (open pericardium) (Leyton, Spotnitz et al. 1971). Right ventricular sarcomere length was linearly related to end-diastolic volume and a curvilinear relationship of sarcomere length to end-diastolic pressure was described (Figure 1.3.3.1.1). Sarcomere length increased from 1.8 microns at a RVEDP of three mmHg, to 2.2 microns at 8 mmHg. Further increases in sarcomere length were achieved only at the expense of very large increases in end-diastolic pressure: a length of 2.4 microns was achieved at a RVEDP of 20 mmHg.

At a sarcomere length of 1.6 microns, wall tension is zero (Thys, Dauchot et al. 1999). However, the sarcomere tension length relationship is very steep. Thus, the peak of the length-tension curve for papillary muscle corresponds to a sarcomere length of 2.2 microns. This sarcomere length corresponds to "the normal upper limit of diastolic filling pressure" in both the right (8 mmHg) and the left ventricles (12 to 15 mmHg) (Leyton, Spotnitz et al. 1971). This means that both the right and left ventricles function along the ascending limb of the length tension curve (Figure 1.3.3.1.1c) and normally operate at end-diastolic sarcomere lengths of 2.24 microns or less (Leyton, Spotnitz et al. 1971). The lower pressure needed in the right versus the left ventricle to attain a similar sarcomere length is accounted for by the right ventricular wall being thinner and therefore more compliant than that of the left ventricle (Figure 1.3.3.1.3) (Leyton, Spotnitz et al. 1971).

However, it is interesting to note that at high right ventricular end-diastolic pressures of 15 mmHg, longer sarcomeres were found in the right than the left ventricle. This observation suggests greater potential for slippage of sarcomeres in the right ventricle. This phenomenon can be observed in Figure 1.3.3.1.1c. If left and right ventricular sarcomere length are compared at high filling pressures, maximal lengthening of sarcomeres first occurs in the middle of either ventricle at a pressure of 8 to 10 mmHg (Leyton, Spotnitz et al. 1971). Further lengthening subsequently occurs at other points in the ventricle, this being a method of a recruiting further preload reserve (Thys and Dauchot 1998; Braunwald, Ross, Jr. et al. 1967).

In a human study, RVEDVI correlated the best with cardiac index (r^2 = 0.56) whereas RVEDP (r^2 = 0.07) and pulmonary artery wedge pressure (PAWP) (r^2 = 0.1) correlated poorly with cardiac output (Conrad 2001). It must be emphasized that the right ventricle is a volume displacement pump and is highly dependent on being adequately filled (Boldt, Kling et al. 1990).

Squara and colleagues (Squara, Journois et al. 1997) developed a novel approach to RV preload. They evaluated end-diastolic RV elastic energy as an index of RV preload. The advantages of using elastic energy as an index of

preload are:

- Firstly, it integrates all the stretching effects of venous return and,
- Secondly, it can be relatively easily measured from the area under the diastolic RV pressure-volume curve.

This method involves measuring the RVDV and RVEDP changes on administration of a fluid bolus. This information is then used to construct a diastolic pressure-volume curve. From the laws of conservation of energy, the (elastic) energy distending the RV should equal the energy contained in the venous return. This may be expressed mathematically:

$$\text{Elastic energy} = \int_{0}^{\text{end diastole}} P \times dV \quad \text{..... Equation 1.3.3.1}$$

This method was studied in patients who had just undergone cardiac surgery. These investigators demonstrated that both RV end-diastolic elastic energy and RVEDV were linearly related to right ventricular ejection fraction (RVEF). However, RV filling *pressures* did not correlate with systolic indices of ejection (Hennebry and Gerstenblith 2001; Squara, Journois et al. 1997).

The greater compliance of the RV results in the RV having a larger EDV than that of the LV (Wiedemann and Matthay 1997; Rigolin, Robiolio et al. 1995). Since both ventricles eject a similar stroke volume, the RV normally has a lower ejection fraction than that of the LV (Rigolin, Robiolio et al. 1995).

End-diastolic pressure of the ventricle is commonly substituted as an index of the end-diastolic volume of the ventricle (Thys and Dauchot 1998). The relationship of diastolic pressure to volume of the ventricle is governed by the diastolic compliance of the ventricle, pericardial and intrathoracic pressures, and the position of the interventricular septum (Table 1.3.3.1) (Dodson, Nathan et al. 1997; Rigolin, Robiolio et al. 1995; Hines and Barash 1993; Weber, Janicki et al. 1983). The resulting relationship between the filling pressures of the two ventricles in normal hearts is such that pulmonary artery wedge pressure is consistently found to be double central venous pressure, and the change in pulmonary artery wedge pressure is double that of the central venous pressure during fluid challenges (Figure 1.3.3.1.3) (Benumof 1998). Thus, less stroke work (essentially the product of pressure and volume generated by a ventricle) can be generated for similar increases in right than left ventricular filling pressure (Figure 1.3.3.2.1) (Randall and Stacy 1956).

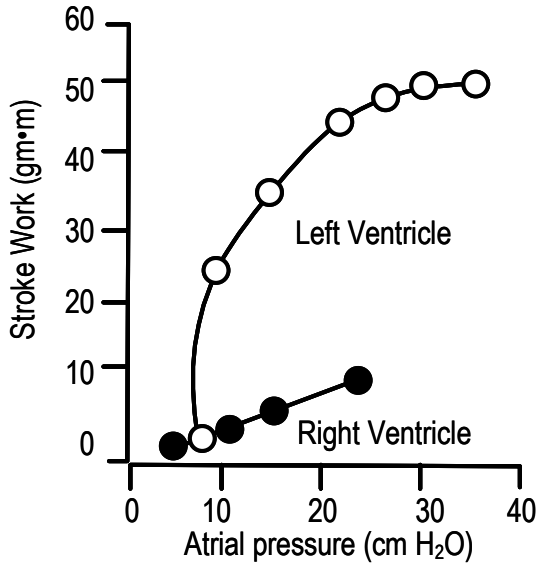


Figure 1.3.3.2.1. Comparative effects of increasing left and right atrial pressure on right and left ventricular stroke work. Wiedemann and Matthay, 1997 and Hines and Barash, 1993

Factors influencing diastolic ventricular properties	
Factors extrinsic to the ventricle	**Factors intrinsic to the ventricle**
1. Pericardium	1. Passive compliance of the ventricular wall (thickness, composition)
2. Loading of the other ventricle and position of the septum	2. Active relaxation (diastolic function) of the ventricular muscle due to residual cross bridging of actin and myosin. Ischemia would deleteriously influence this factor
3. Intrathoracic pressure	3. Elastic recoil (diastolic suction)

Table 1.3.3.1 Adapted from Braunwald et al, 1998

The compliance of the RV results in an end-diastolic pressure that hardly changes over the physiological range (Hennebry and Gerstenblith 2001). This can be deduced from inspecting the initial flat part of the ventricular diastolic pressure-volume relationship (Figure 1.3.4.1[#]) (Braunwald, Sonneblick et al. 1998; Stoltzfus 1997). The flat portion of the diastolic pressure-volume curve where the pressure doesn't rise is analogous to the filling of a large rubber balloon. The initial inflation does not stretch its floppy walls. It is only after the balloon has been inflated to the point that the walls start to stretch that a rise in distending pressure can be measured. In other words, initial EDP of the RV is poorly related to its EDV (Diebel, Wilson et al. 1992; Dhainaut and Squara 1992; Martyn, Snider et al. 1981). Investigators consistently show that due to this poor correlation of EDP to EDV, the indices of forward flow are better related to right ventricular EDV than to EDP (Martyn, Snider et al. 1981). Nevertheless some sources do report that CVP is a good indicator of RVEDV (Thys and Dauchot 1998).

Filling of the right ventricle occurs in phases and is not purely passive. In early diastole, the ventricle creates a mild suction that aids the inflow of blood (Shintani and Glantz 1994a). However later in diastole, atrial contraction contributes up to 25 percent to filling in the normal ventricle (Stoltzfus 1997): this allows lower mean atrial and venous pressures than would be the case if the atrial contraction was not present (Braunwald, Sonneblick et al. 1998). Atrial contraction is of lesser importance in the presence of normal RV physiology. However, the less compliant a ventricle becomes, the greater the atrial contribution to the EDV and the greater the contribution that atrial contraction makes to ventricular filling (Thys and Dauchot 1998; Braunwald, Sonneblick et al. 1998).

Factors that govern the passive return of blood to each chamber are different. The pressure gradient governing the

[#] Albeit Figure 1.3.4.1 depicts the LV, it illustrates the situation that would occur in the RV with and without the pericardium intact. The reader is pointed to LeWinter, Myhere et al. 1994 for examples of RV pressure-volume relationships with and without an intact pericardium that are similar to that illustrated in Figure 1.3.4.1.

passive flow of blood to the right ventricle is the difference between intra- and extra- thoracic pressures. The venous return to the left ventricle is determined by the pulmonary venous drainage. This process occurs within the thoracic pressure chamber. That gradient is not deleteriously affected by increases in intrathoracic pressure, as is the situation with the RV.

Preload is normally *the* major determinant of stroke volume in both ventricles (Hennebry and Gerstenblith 2001; Reuse, Vincent et al. 1990). However, the importance of preload may eventually be overshadowed when the right ventricle experiences a significant increase in afterload.

1.3.4 The pericardium

The pericardial collagen bundles are wavy and stretch easily until tractional forces cause them to straighten. At this point the pericardial tissue becomes relatively inelastic (Figure 1.3.4.1) (Shintani and Glantz 1994b). Above the point that it is relatively non-elastic, the pericardium is stiffer than the myocardium and presents considerable resistance to attempts to increase its volume or the volume of the underlying ventricles (Shintani and Glantz 1994b). Above this inflexion point, the pericardium will govern the diastolic pressure-volume relationship of the normal right ventricle. The inflexion point occurs at an end-diastolic pressure of between 3 to 8 mmHg for the right ventricle (Shintani and Glantz 1994b; Milnor 1982c) and 10 mmHg for the left ventricle (Shintani and Glantz 1994a).

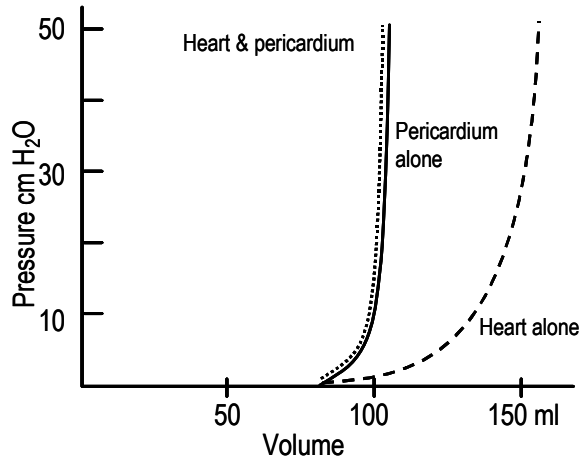


Figure 1.3.4.1. Pressure volume relationships of the heart and pericardium, together and alone. The heart without the pericardium is far less stiff then the two together. The two together is virtually the same as the pericardium alone, indicating that the stiffness of the pericardium dominates the curve for the ventricle alone, especially along the steeper part of the pressure volume curve. Redrawn from Shintani and Glantz, 1994

The magnitude of pericardial pressure is similar to right atrial and right ventricular EDP (Shintani and Glantz 1994b; Calvin 1991). In other words, pericardial and RV end-diastolic pressures increase in approximately a one to one relationship (Shintani and Glantz 1994b; Calvin 1991). Therefore pericardial constraint causes the upper limit of end-diastolic volume (and hence stroke volume) of the normal right ventricle to be reached at an end-diastolic pressure of 12 (Weber, Janicki et al. 1983) to 15 (Stoltzfus 1997) mmHg. This underscores the importance of the pericardium on limitation of right ventricular filling in the normal heart (Shintani and Glantz 1994b). This limitation is quantitatively different for the left and right ventricles because of the right ventricle being more compliant than its counterpart. Therefore, at any particular pericardial pressure, right ventricular filling will be influenced to a greater degree than left ventricular filling (Shintani and Glantz 1994b).

Opening the pericardial sac during right ventricular infarction in dogs removes a major limitation on RV dilation. This results in the ability to increase both the right and left ventricular end-diastolic volumes and permit the generation of larger stroke volumes (Shintani and Glantz 1994a; Calvin 1991). Opening the pericardium has a further effect of causing the ventricular diastolic pressure-volume relationship to shift down and to the right (i.e. becomes more compliant – Figure 1.3.5.1): This has a more marked effect on the right than on the left ventricular diastolic pressure-volume relationship (Calvin 1991).

The role of the pericardium on systolic pump function in man has been a subject of debate (Shintani and Glantz 1994b). Some studies have found that the pericardium does not influence the systolic function of either ventricle (Shintani and Glantz 1994b; Mangano 1980). This differs from other studies where the pericardium has been demonstrated to limit ventricular expansion and subsequent generation of right ventricular stroke work. The explanation for the difference in these studies may lie therein that cardiac dilatation takes a (short) period of time to occur, and only then tests the limits of pericardial expansion (Shintani and Glantz 1994b). During the period before these limits are reached, the pericardium will play no role on filling of the RV. Nonetheless, the situation during chronic ventricular dilation may be different. The pericardium may stretch over time and accommodate a larger volume. This stretch will result in loss of hemodynamic findings associated with subsequent volume loading or episodes of dilatation (Shintani and Glantz 1994b; Mangano 1980).

1.3.5 Ventricular interaction

The two ventricles are encircled by common muscle fibres, share a septal wall and are enclosed within the pericardium (Santamore and Gray, Jr. 1996). This intimate anatomical association causes the ventricles to interact mechanically with each other (Santamore and Gray, Jr. 1996; Shintani and Glantz 1994a; Santamore, Lynch et al. 1976a; Santamore, Lynch et al. 1976b; Taylor, Covell et al. 1967). Santamore and Gray define this interaction as the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral or circulatory effects (Santamore and Gray, Jr. 1996). The ventricle-ventricle interaction has been the most extensively studied relationship, albeit that inter-atrial and atrio-ventricular interactions also exist (Santamore and Gray, Jr. 1996; Shintani and Glantz 1994b). Ventricular interaction is commonly divided into diastolic and systolic, or parallel and series interactions.

The left and right ventricles are a set of pumps in series that eject the same cardiac output over a short period of time (Santamore, Lynch et al. 1976b). The implications of this are twofold. Firstly, the right provides at least part of the energy needed to fill the left ventricle during diastole (Piene 1986). Secondly, right ventricular output becomes the left ventricular output after passing through the pulmonary circulation (Shintani and Glantz 1994a). Should right ventricular output decrease, the left ventricle will become underfilled. This consequence is termed a **series** interaction between the ventricles.

The relationship of mechanical forces across the interventricular septum on ventricular function is termed **parallel** or **direct** ventricular interaction (Shintani and Glantz 1994b). **Diastolic** ventricular 'crosstalk' is the best-studied interaction (Shintani and Glantz 1994b). Ventricular-ventricular interaction is particularly dynamic in diastole when pressures and wall stresses are low (Shintani and Glantz 1994a). Santamore and Gray (Santamore and Gray, Jr. 1996) and others emphasize that the shape and position of the septum at the onset of systole is extremely sensitive

to small alterations in the end-diastolic transseptal pressure gradient (Dodson, Nathan et al. 1997; Rigolin, Robiolio et al. 1995; Hines and Barash 1993; Weber, Janicki et al. 1983; Kingma, Tyberg et al. 1983). It has been stated "*diastolic ventricular interdependence is present on a beat to beat, and moment to moment basis as part of the measured diastolic pressure of the ventricle is caused by the opposite ventricle. However, ventricular interdependence is most apparent with sudden changes in ventricular volume"* (Santamore and Gray, Jr. 1996). Thus, the interventricular septum normally bows convexly into the right ventricle. This is dependent on a positive left to right diastolic pressure gradient (Figure 1.6.2.3) (Kingma, Tyberg et al. 1983). If the normal gradient is reduced (e.g. an increase in RV end-diastolic volume or pressure) progressive flattening of the septal curvature occurs. When the gradient is reversed, the septum will bulge into the left ventricle, distort its geometry and reduce its compliance (Figure 1.3.5.1) (Shintani and Glantz 1994b; Kingma, Tyberg et al. 1983; Santamore, Lynch et al. 1976a).

Taylor et al. (Taylor, Covell et al. 1967), and Santamore et al. (Santamore, Lynch et al. 1976a) investigated diastolic ventricular interaction by varying right ventricular volume while keeping the left ventricle at various constant volumes. For a given right ventricular end-diastolic volume, the corresponding filling pressure was dependent on the left ventricular end-diastolic volume (Figure 1.3.5.2) (Wiedemann and Matthay 1997; Shintani and Glantz 1994a; Calvin, Jr. 1991; Weber, Janicki et al. 1983; Taylor, Covell et al. 1967). These studies were performed without the pericardium. It is however known that ventricular interaction is markedly amplified by the intact pericardium, because changes in ventricular pressure and volume are associated with similar trends in intrapericardial pressure (Shintani and Glantz 1994b). These studies may therefore underestimate the magnitude of this effect.

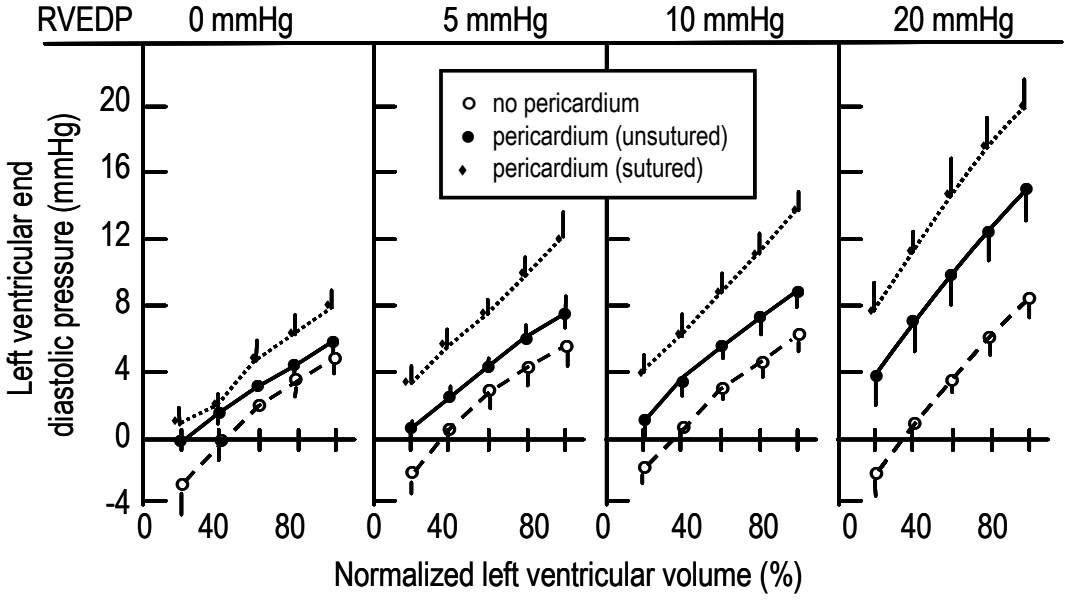


Figure 1.3.5.1. The effect of RVEDP on LVED pressure-volume relationships is amplified by an intact pericardium. RVEDP was raised in a stepwise fashion. At each RVEDP, incremental increases in left ventricular volumes were made and the LV pressure-volume relationship measured at each incremental change. When the pericardium is intact, the P-V relationships are shifted upward compared to when the pericardium is absent. A further increase is seen when the pericardium is sutured. Rigolin, Robiolio et al, 1995

The diastolic interventricular relationship has moreover been quantified (Shintani and Glantz 1994b). The magnitude of the interaction can be expressed as the gain in RV pressure (ΔP_{RV}) secondary to changes in LV pressure (ΔP_{LV}) for an unchanged LV volume:

$$G_{R \rightarrow L} = \Delta P_{LV} / \Delta P_{RV}$$

Where $G_{R \rightarrow L}$ is the right to left ventricular crosstalk gain (Hennebry and Gerstenblith 2001).

The change in LVEDP for a given change in RVEDP ($G_{R \rightarrow L}$) is 0.33. This value is independent of the absolute EDP, and implies that a linear relationship exists between the two ventricles (Shintani and Glantz 1994b).

What are the implications of diastolic ventricular interaction on the systolic function of the other ventricle? An increase in EDP or EDV of one ventricle results in the other ventricle having a reduced EDV with a decrease in stroke volume and systolic pressure for the same contractile state and afterload (Shintani and Glantz 1994b; Santamore, Lynch et al. 1976a; Santamore, Lynch et al. 1976b). Furthermore, the changing compliance of the other ventricle means that its end-diastolic pressure is not a good reflection of either end-diastolic volume or sarcomere length (Taylor, Covell et al. 1967). Santamore has also demonstrated that the left ventricular pressure-volume relationship is influenced not only by the volume of the opposite ventricle, but can be modified exclusively by changes in RV pressure and compliance (Shintani and Glantz 1994a; Santamore, Constantinescu et al. 1988a; Santamore, Constantinescu et al. 1988b).

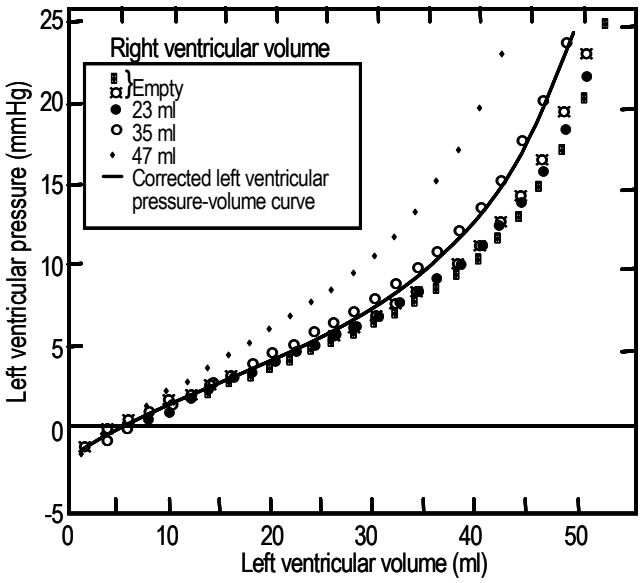


Figure 1.3.5.2. Left ventricular diastolic pressure-volume relationship at various levels of right ventricular filling in the dog with the pericardium removed. Redrawn from Taylor, Covell et al, 1967

The relative importance of the parallel versus the series interaction between the ventricles has been difficult to study (Shintani and Glantz 1994a). Nonetheless, it has been concluded that parallel interaction is about half as important as series interaction in determining LV end-diastolic volume when the pericardium is present. Removing the pericardium decreases the importance of parallel interaction to about one fifth that of the series effect (Slinker and Glantz 1986).

The relative importance of the parallel versus the series interaction depends also on the stiffness of the ventricular walls. In hypertrophied hearts with an intact pericardium, parallel interaction is only one tenth as important as the series interaction in determining ventricular EDV. This is understandable as the thick non-compliant ventricular walls and septum are resistant to external influences (Shintani and Glantz 1994a; Shintani and Glantz 1994b). Removal of the pericardium in subjects with ventricular hypertrophy makes little difference to the relative importance of the series versus parallel interaction discussed above (Shintani and Glantz 1994a; Slinker, Chagas et al. 1987).

LeWinter and colleagues have recently observed an interesting ventricular interaction whereby a small decrease in caval flow and RVEDV occurs when LVEDV increases suddenly (Shintani and Glantz 1994b). This may be secondary to a decrease in the pressure gradient responsible for venous return to the RV.

The left ventricle dominates the systolic interplay between the ventricles (Weber, Janicki et al. 1983; Elzinga, Piene et al. 1980). The pressure generated by the left ventricle during systole has been shown to cause a double peak in the RV pressure waveform. What is remarkable is that the transmission of force to the RV contributes significantly to pulmonary artery blood flow (Santamore and Gray, Jr. 1996; Shintani and Glantz 1994a; Damiano, Jr., La Follette, Jr. et al. 1991; Weber, Janicki et al. 1983; Elzinga, Piene et al. 1980; Santamore, Lynch et al. 1976a; Santamore, Lynch et al. 1976b). Quantification of these components suggests that the left ventricular component is significantly greater than that of the right ventricle. Thus, peak systolic pressures of 63.5% vs. 36.5%, root mean squared values of 65.5 vs. 34.8%; and pulmonary blood flow 67.5 vs. 32.5% were associated with the left and right ventricular components respectively (Table 4.3.3) (Santamore and Gray, Jr. 1996; Damiano, Jr., La Follette, Jr. et al. 1991). It follows that when right ventricular free wall performance is acutely depressed, the RV function of propelling blood through the pulmonary vasculature is even more dependent on left ventricular-septal contraction (Shintani and Glantz 1994a). In addition, the maintenance of circulatory function after inactivation of the RV free wall is testimony of the left ventricle being operative in sustaining right ventricular performance (Sunagawa, Maughan et al. 1983; Santamore, Lynch et al. 1976b; Donald and Essex 1954; Kagan 1952; Starr, Jeffers et al. 1943).

The mechanism of systolic ventricular interaction has been discussed in the literature. The generation of transseptal pressure gradients has been suggested to play an important role in systolic ventricular interdependence (Santamore and Gray, Jr. 1996; Sunagawa, Maughan et al. 1983; Santamore, Lynch et al. 1976b). However Santamore and Gray suggest that ventricular pressures and volumes are really the consequence of stress in the ventricular walls and that "ventricular interdependence should really be viewed as the balance of forces at the interventricular sulcus" (Figure 1.3.5.3) (Santamore and Gray, Jr. 1996).

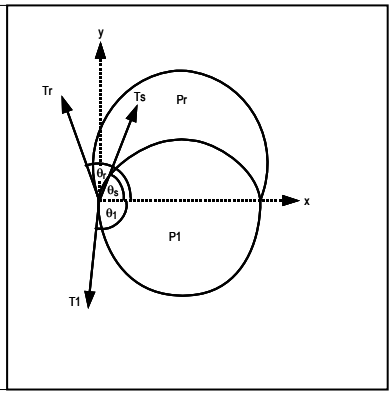


Figure 1.3.5.3. The diagram illustrates the balance of forces at the interventricular sulcus. The summation of the forces at the sulcus is zero. The tension in the LV free wall (T1) is balanced by tension in the septum (Ts) and the RV free wall (Tr). The force in the LV free wall is balanced by forces in the RV free wall and interventricular septum. Therefore changing one wall directly affects all three walls: i.e. a direct transfer of forces between the left and right ventricular free walls occurs. If the LV volume changes, it will affect both LV free wall and septum, and the RV free wall dimensions. Adapted from Santamore and Gray, 1996

Weber and colleagues have suggested that the systolic function of the RV only affects left ventricular contraction when its RV systolic pressure approximates that in the left ventricle (Weber, Janicki et al. 1983). Other work (Shintani and Glantz 1994b; Calvin, Jr. 1991) has quantified this interaction on left ventricular systolic function. Pulmonary artery constriction results in a small amount (4 to 10%) augmentation increase in LV pressure and stroke volume (Hennebry and Gerstenblith 2001; Shintani and Glantz 1994b).

1.3.6 Myocardial blood supply to the right ventricle

The RV is supplied predominantly by the right coronary artery (Stoltzfus 1997; Rigolin, Robiolio et al. 1995; Dries and Mathru 1992). Various factors result in the right ventricle being better protected against ischemia than the left ventricle (Hines and Barash 1993):

1. The right ventricle receives coronary supply in both systole and diastole, whereas the LV coronary blood flow occurs predominantly in diastole. Faster heart rates with shorter diastolic filling times will interfere less with RV coronary blood flow.

2. Autoregulation prevents the lion's share of blood from going to the right ventricle as would happen if only hydraulic factors played a role in blood flow distribution between the ventricles. Furthermore, the flow per gram of tissue in the RV is only two thirds of that of the left ventricle (Dries and Mathru 1992).

3. The right ventricle is able to receive nutrient flow directly from the Thebesian veins, which is not possible on the left hand side of the heart (Stoltzfus 1997).

4. Extensive collateral connections have been shown to develop when right coronary artery obstruction occurs. The moderator band[#] artery is a branch of the LAD. This artery is suggested to be an important source of blood to the RV papillary muscles and to part of the RV free wall during obstruction of the proximal RCA. Collateral flow via the moderator band artery protects against right ventricular infarction (Hines and Barash 1993; Sunagawa, Maughan et al. 1985).

5. The systolic and end-diastolic pressures, and therefore the wall tension, are lower in

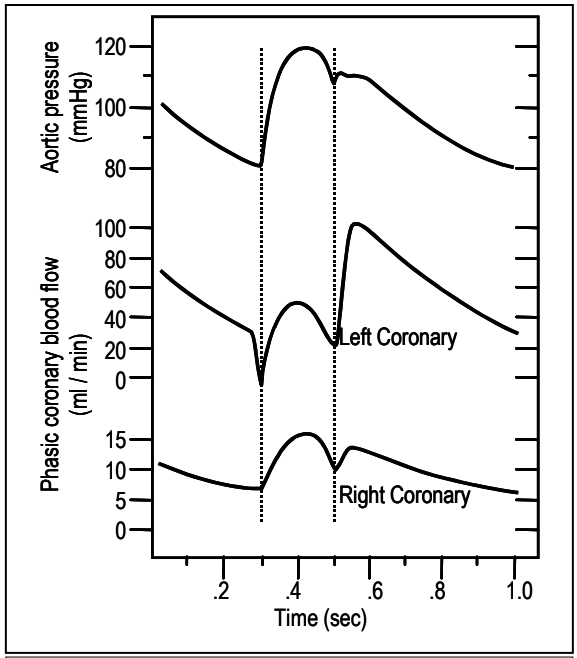


Figure 1.3.6.1. Coronary blood flow during one cardiac cycle. The majority of LV CBF occurs during diastole and the majority of RV CBF occurs during systole. Redrawn from Thys and Dauchot, 1998

[#] The moderator band is one of the trabeculae that are better developed than the rest (Hurford and Zapol, 1988).

the right than the left ventricle. This results in lower oxygen requirements and oxygen extraction. Furthermore, RV subendocardial blood supply is relatively greater than that of the LV. This is important in the prevention of RV ischemia, as the subendocardium is an especially vulnerable portion of both the left and right ventricles (Dries and Mathru 1992). Nonetheless, the closer the RV pressure approximates systemic pressure, the more the RV behaves like the left ventricle in terms of coronary blood flow (Figure 1.3.6.1) (Rigolin, Robiolio et al. 1995; Hines and Barash 1993; Dhainaut and Squara 1992; Milnor 1982).

The relationship between ventricular work performed and myocardial oxygen consumption is termed myocardial efficiency (Hennebry and Gerstenblith 2001). The RV normally operates at maximal efficiency, as does its counterpart, the LV.

1.4 Afterload and the right ventricle

The concept of afterload was introduced by Starling to distinguish phenomena relating to emptying from that of filling of the ventricle (Noordergraaf and Melbin 1978). The right ventricle has been suggested to be very sensitive to afterload, much more so than the left ventricle (Hennebry and Gerstenblith 2001).

Afterload is easy to define for an isolated muscle preparation, but is considerably more complex to define for the intact heart. Braunwald defines afterload in isolated papillary muscle as being the force resisting muscle fibre shortening (Braunwald, Ross, Jr. et al. 1967). From inspection of Figure 1.4.1, it can be seen that afterload is the tension that a contracting muscle must develop before shortening can occur (Hurford and Zapol 1988). Furthermore, an inverse relationship exists between the velocity of myocardial fibre shortening and afterload (Figure 1.4.1 c and d) (Thys and Dauchot 1998; Braunwald, Sonneblick et al. 1998; Milnor 1982a; Braunwald, Ross, Jr. et al. 1967). The implication is that as the afterload on cardiac muscle increases, the ability of isolated muscle preparations to shorten and perform work decreases progressively (Figure 1.4.1 f).

Afterload in the intact heart has been described in the following terms (Thys and Dauchot 1998; Hurford and Zapol 1988):

- Ventricular pressure,
- Wall stress,
- Vascular resistance,
- Input impedance and,
- Arterial elastance (E_a).

Milnor suggests that there are two main schools of thought as to just what constitutes the afterload on the intact ventricle. The first, which is derived from experiments using isolated muscle strips, suggests that afterload is the pressure (alternatively wall tension or stress) developed by the ventricle (Milnor 1982a). This has been referred to the *internal* resistance of the ventricle.

A second way of looking at afterload is that of forces external to the ventricle as being the load that opposes ventricular ejection (Thys and Dauchot 1998; Milnor 1982a).

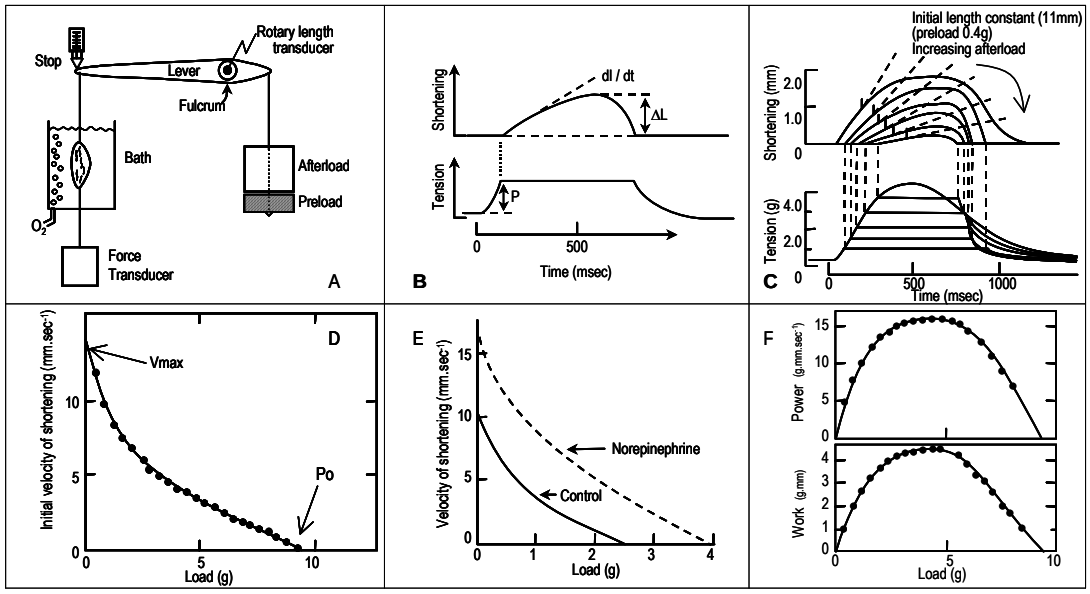


Figure 1.4.1 *The use of afterloaded isotonic contractions to obtain force-length relationships. Adapted from Braunwald, Ross et al, 1967; Braunwald, Sonneblick et al, 1998; Milnor, 1982 and Thys and Dauchot 1998*

A. A papillary muscle is placed in a bath of Ringers solution and stimulated by electrodes. The lower end of the muscle is attached to an extension from a tension (force) transducer. The upper end is attached to the end of a lever system that is free to move. The stop is not initially placed above the lever. A small weight that constitutes preload stretches the muscle to its resting length. The stop is now fixed above the tip of the lever; the result of fixing the stop is that the muscle does not sense any weight added to the counterbalance until it begins to contract. Total load equals the sum of preload and afterload.

B. A tracing of an afterloaded isotonic contraction. The contraction is shown as a function of tension and shortening versus time. After stimulation at time zero, there is a short latent period. This latent period is followed by isometric contraction until the force (P) just exceeds the load when shortening begins. Maximum velocity is reached soon after the shortening begins. The tangent to the shortening slope (dl/dt) is the maximum velocity of shortening for that particular load.

C. Muscle shortenings are shown for progressive increases in afterload with preload kept constant. Increasing afterload decreases both the velocity of shortening (dl/dt), and the extent of the shortening.

D. The velocity of shortening (dl/dt) is plotted as a function of afterload. This is termed the force-velocity relationship. As the afterload is increased, the velocity of shortening increases. An inverse relationship exists between afterload (load) and the initial velocity of shortening of cat papillary muscle. When the curve is extrapolated back to zero load, Vmax is obtained. Increases in initial muscle load (preload) do not alter Vmax. However, the maximal force that the papillary muscle can develop (Po) increases as the preload exerted on the muscle increases (not illustrated).

E. When contractility is increased, the rate of tension development and the extent of shortening for a given afterload increases significantly. The whole curve is shifted upwards and to the right and both Vmax and Po increased\. (Vmax therefore is an index of the contractile state of the muscle.)

F. The top graph illustrates the relationship between afterload and power (the product of load and velocity) done by the papillary muscle. The bottom graph illustrates the relationship between afterload and work (the product of load and length) done by the papillary muscle. For a particular pump and its load, maximum work is done at the summit of the curve. When the pump operates at that point, the pump is considered matched to its load. Should the working point move to the right or left, then less work is done and the pump and its load are not optimally matched.

The pressure generated by the ventricle comprises a component of each of the above definitions of afterload, and it will not be dealt with as a separate topic. Similarly trends emerge in isolated muscle facing an increase in afterload and the RV facing an increase in afterload. An inverse relationship exists between stroke volume and the pressure developed by the right ventricle (Figure 1.4.2.2.1). At pulmonary artery pressures that were acutely raised to 63 and 80 mm Hg systolic, the right ventricle was unable to eject blood (Weber, Janicki et al. 1983). It has been suggested that the right ventricle is twice as sensitive as the left ventricle to similar percentage rises in the ejection pressure (Weber, Janicki et al. 1983; Stool, Mullins et al. 1974). A similar inverse relationship was subsequently described between PVR and right ventricular stroke volume (Figure 1.4.2.2.1) (Piene and Sund 1979). Qualitatively similar function and curves have been described for the left ventricle facing an increase in afterload (Thys and Dauchot 1998).

1.4.1 Wall stress (σ) as afterload

The law of Laplace, when applied to the ventricle, states that the forces within the ventricular wall are functions of the intraventricular pressure and geometry (size and shape and thickness) of the chamber (Shintani and Glantz 1994a; Sandler and Dodge 1963). The nature of these forces is illustrated in Figure 1.4.1.1. If a hypothetical slit were made in the ventricular wall, the edges would pull apart with a certain force per centimetre per length of the slit. The force per unit length of slit is defined as wall tension[1] (Sandler and Dodge 1963). In other words, wall tension is the force per centimetre length in a circumferential strand of myocardium in a particular plane (Figures 1.4.1.1) (Thys and Dauchot 1998). The units of tension are grams.cm^{-1} or dynes.cm $^{-1}$ (Thys and Dauchot 1998).

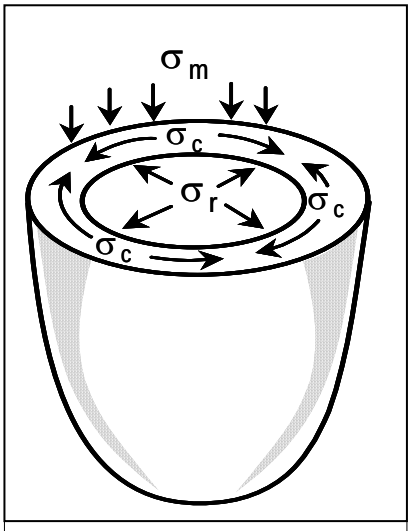


Figure 1.4.1.1. Circumferential (σ_c), meridional (σ_m) and radial (σ_r) components of wall stress in an ellipsoid model of a ventricle. The three components are mutually perpendicular and not significantly different from each other. Redrawn from Thys and Dauchot, 1998 and Lang, Borow et al, 1986

Because the wall has a thickness too, the hypothetical slit described above creates an area in the wall (Figure 1.4.1.2) (Sandler and Dodge 1963). Wall stress σ is defined as the force exerted per cross sectional area of ventricular wall (Thys and Dauchot 1998; Shintani and Glantz 1994a; Sandler and Dodge 1963). Stress is expressed in units of grams.cm^{-2} or dynes.cm^{-2}. The mathematical relationship between stress and tension is that tension is the product of wall stress and wall thickness (Sandler and Dodge 1963).

To model the concept of wall stress as afterload, the (left) ventricle can be viewed as a pressurized spherical shell (Shintani and Glantz 1994a). Three assumptions that allow us to derive an equation for wall stress are (Shintani and Glantz 1994a):

[1] The word tension is often used to convey different meanings: Force per unit length as in surface tension (dynes.cm^{-1} or g.cm^{-1}) or force per unit area as in stress (dynes.cm^{-2} or g.cm^{-2}) or as another word for force (dynes or grams). Note that 1 gram is equal to 981 dynes.

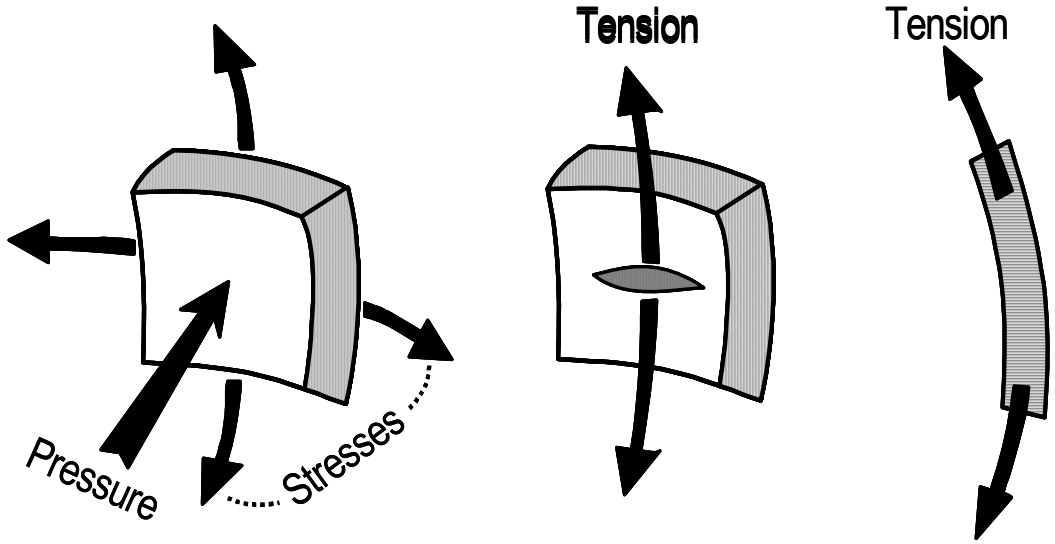


Figure 1.4.1.2. Stress and tension in the ventricular wall. Sandler and Dodge, 1963

The ventricle is a sphere with a uniform wall thickness, *h* and inner radius *r*;

1. The ventricle is stationary and,
2. The wall is so thin that the stress is constant throughout the wall.

To start with, we may cut the sphere into two halves to expose the internal forces. The force tending to push the hemispheres away from each other is equal to the pressure within the sphere multiplied by the cross-sectional area, πr^2 (Shintani and Glantz 1994a). Alternatively, the total force *in the wall* holding the two halves together equals the wall stress (σ) multiplied by the cross-sectional area of the wall.

The force within the sphere pushing the two halves away is

$$P\pi r^2 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.1.1}$$

The force within the wall holding the two halves together can be considered to be

$$\sigma\pi [(r+ h)^2 - r^2] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.1.2}$$

These two forces must balance, therefore

$$P\pi r^2 = \sigma\pi [(r+ h)^2 - r^2] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.1.3}$$

Because we assumed a thin wall, the ratio of the thickness to the internal radius is very small (at least, much smaller than 2), we can ignore h/r. If we then solve for stress, we get

$$\sigma = Pr/2h \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.1.4}$$

Where

σ is the wall stress,

P is the pressure in the ventricle,

r is the radius of the ventricle and,

h is the thickness of the ventricle

It should be noted both wall stress and tension vary with time: this is because P, r, and h are dimensions that vary during the cardiac cycle (Sandler and Dodge 1963). Different components of systolic wall stress have been identified, each of which has its own importance (Lang, Borow et al. 1986):

1. Peak systolic wall stress: this is the most important stimulus for ventricular hypertrophy in the face of pressure overload faced by a ventricle.
2. The integral of systolic wall stress over time ($\int Tdt$): $\int Tdt$ correlates closely with myocardial oxygen consumption (Lang, Borow et al. 1986; Sandler and Dodge 1963). (i.e. both wall stress and the time over which this stress is exerted determine oxygen consumption). Acute increases in wall stress faced by the right ventricle therefore play a role in inducing imbalances in its oxygen supply-demand ratio (Martyn, Snider et al. 1980).
3. End systolic wall stress (σ_{es}): σ_{es} defines the force limiting ventricular fibre shortening. Wall stress at the end of systole, and not the stress during the ejection phase, is inversely related to the velocity and extent of fibre shortening in the ventricle (Lang, Borow et al. 1986). This is analogous to the inverse relationship that exists between the velocity of myocardial fibre shortening and afterload observed in isolated muscle preparations (Braunwald, Sonneblick et al. 1998). It is reasonable to speculate that if similar relationships apply to the isolated cardiac muscle and left ventricle, that such a relationship would apply to the right ventricle.

From the formulae derived above, it follows that P, r, and h play a significant role in influencing wall stress. Wall stress reaches its peak during the first third of systole, a period when the ventricle still contains its end-diastolic volume. This peak occurs despite the ventricular pressure rising throughout the ejection period. This emphasizes the importance of the increase in wall thickness and the decrease in volume of the ventricle in limiting wall stress. The remodelling of the ventricles that occurs for example, after birth or in response to chronic increases in the pressure they need to generate, is an attempt to normalize peak systolic wall stress (Jackson and Thomas 1998; Lang, Borow et al. 1986; Sandler and Dodge 1963). Left ventricular hypertrophy that occurs in association with aortic stenosis actually normalizes wall tension of the left ventricle (Jackson and Thomas 1998). No such studies of right ventricular hypertrophy and wall stress could be found.

The normal left ventricle is not spherical and approaches the shape of an ellipse. Various radii are therefore present for which different vectors of wall stress (circumferential, meridional and radial) are described (Figure 1.4.1.1) (Thys and Dauchot 1998; Sandler and Dodge 1963). It has been demonstrated that at the equator of the ellipse with radii r_1 and r_2 that:

$\sigma_1/r_1 + \sigma_2/r_2 = P/h$ ..... Equation 1.4.1.5 (Sandler and Dodge 1963)

Where

σ_1 and σ_2 represent the wall stresses at the equator of each half of an ellipse.

Wall stress undoubtedly plays a similar role in both right and left ventricular function (Thys and Dauchot 1998). The right ventricle is crescent shaped and is more difficult to model mathematically (Dhainaut and Squara 1992). The factors determining wall stress have not been formally conceptualised for the RV. Nonetheless, it has been suggested that the two curvatures of its walls may be considered as two separate radii as has been described for the left ventricle (Equation 1.4.1.5), but this concept has not been further discussed in the literature.

When an acute increase in afterload is presented to the right ventricle, it utilizes preload reserve to maintain stroke volume (Calvin, Jr. 1991). This results in both pressure and volume of the ventricle increasing. An increase in end-diastolic volume and therefore radius of the ventricle causes an increase in both wall tension and stress (Jackson and Thomas 1998; Sandler and Dodge 1963). The decrease in wall thickness as the already thin right ventricle dilates, accentuates the rise in wall stress (Calvin, Jr. 1991; Martyn, Snider et al. 1980). The increase in wall tension will lead to an increase in oxygen demand of the RV.

The above discussion emphasizes that intraventricular pressure, radius and wall thickness all play a significant role in determining wall stress. From this perspective, the following points regarding afterload need to be emphasized:

1. The RV free wall is, at most, half the thickness of the LV and the RVEDV exceeds that of the LV. This results in RV wall stress that tends to exceed that of the LV chamber. However, the one factor limiting the development of RV chamber stress is the lower pressure that the RV normally has to generate.
2. Intraventricular pressure is only one component of afterload. If pressure is viewed in isolation, it may give an incorrect impression of afterload (Thys and Dauchot 1998; Lang, Borow et al. 1986).
3. Preload has an effect on afterload. However, the only indices of afterload that are available in the clinical scenario are RVEDV and RV ejection pressure.
4. It is not possible to measure wall tension and stress in the human right ventricle. However, the ability to measure both right ventricular volume and pressure present valuable clinical clues in the evaluation of wall tension and stress (Equation 1.4.1.4).

1.4.2 The arterial system as afterload: pulmonary vascular resistance

Poiseulle (1799-1869) first described the relationship between steady flow and pressure of fluid in cylindrical tubes (Milnor 1982b):

$$Q = \pi r^4 (P_1 - P_2) / 8 \eta L \quad \text{..... Equation 1.4.2.1}$$

Where

- Q is flow in a vessel or tube,
- r is radius of the vessel,
- P_1 is the pressure at the beginning and
- P_2 is the pressure at the end of a tube of length L, and
- η is the viscosity of the fluid.

This equation applies to laminar type flow at a steady flow rate (Parbrook, Davis et al. 1985).

Poiseuille's law may also be considered in the following way: the ratio of the pressure gradient to the flow is a function of the physical properties of the system (dimensions of the tube, and the viscosity of the fluid being moved) (Equation 1.4.2.2). The ratio of pressure gradient to flow rate is therefore a measure of the extent to which the system opposes or resists flow (Milnor 1982b). This ratio, when it is determined for the pulmonary or systemic arterial tree, is called vascular resistance (R). This ratio can be formulated in the following equations:

$$(P_1 - P_2) / Q = 8\eta L / \pi r^4 \quad \text{..... Equation 1.4.2.2}$$

$$R = 8\eta L / \pi r^4 \quad \text{..... Equation 1.4.2.3}$$

$$(P_1 - P_2) / Q = R \quad \text{..... Equation 1.4.2.4}$$

Vascular resistance (Equation 1.4.2.3) is analogous to electrical resistance as described by Ohm's law (Equation 1.4.2.5) (Parbrook, Davis et al. 1985; Milnor 1982b)

$$\text{Electrical resistance} = E / I \quad \text{..... Equation 1.4.2.5}$$

Where

E is the flow of current through a circuit component, and

I is the decrease in voltage across the system.

If Equation 1.4.2.4 is applied to humans, it assumes that the cardiovascular system is a direct current circuit. Thus, for steady flow in a system of smooth walled similar non-distensible tubes in which flow is laminar, resistance to flow will be constant. The graph of pressure versus flow is linear and the gradient represents resistance. A steep gradient indicates that the resistance is high and vice versa.

Calculations of vascular resistances are easily done in clinical medicine (Equations 1.4.2.6 and 1.4.2.7). This ease adds to the clinical appeal of this number. However, flow (cardiac output) in clinical practice is usually measured as time averaged or mean flows (Nichols, Conti et al. 1977). The values for pressure are also not instantaneous, but mean pressures. These values do not reflect the fact that flow and pressure varies during the cardiac cycle. The implication is that calculating resistances based on average values cannot be a truly representative index of opposition to flow in the vasculature.

$$SVR = MAP - CVP / CO \quad \text{..... Equation 1.4.2.6}$$

$$PVR = PAP - PAWP / CO \quad \text{..... Equation 1.4.2.7}$$

Where

SVR is systemic vascular resistance;

PVR is pulmonary vascular resistance;

CVP is central venous pressure;

PAWP is pulmonary artery wedge pressure and,

CO is cardiac output in litres per minute.

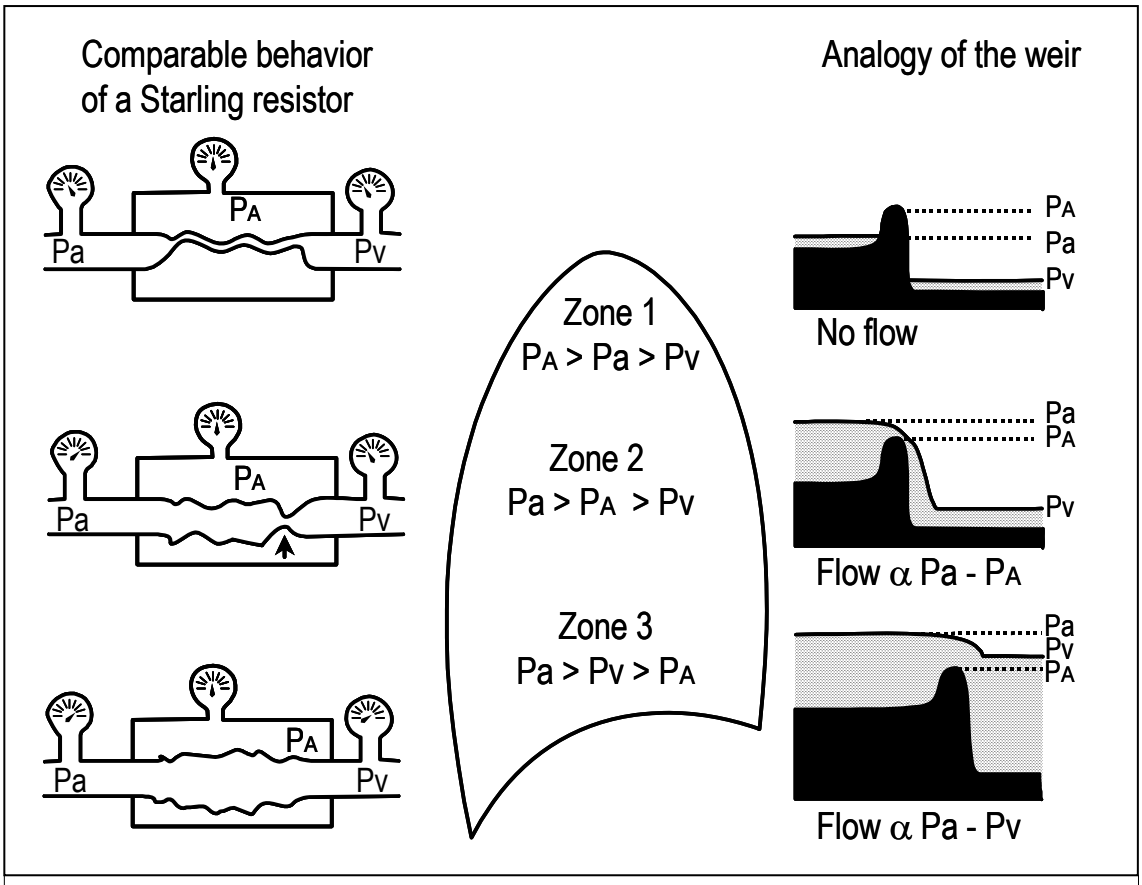


Figure 1.4.2.1.1. The effect of gravity on PVR is compared with a Starling resistor (left) and with a weir (right). Redrawn from Nunn, 1988

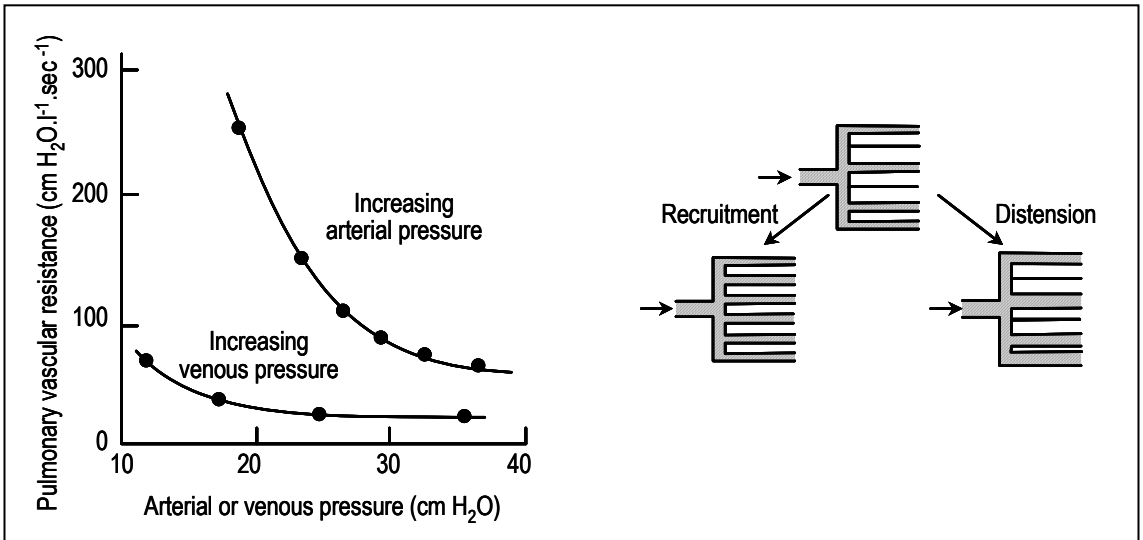


Figure 1.4.2.1.2. Left: Pulmonary vascular resistance decreases as pulmonary arterial or venous pressures are raised. Right: Recruitment and dilation are the reasons given as to why PVR decreases as pulmonary vascular pressures decrease. West, 1985

1.4.2.1 The factors determining normal pulmonary vascular resistance

It is useful to consider the resistance met by the blood flowing through the lungs (PVR) as the difference between pulmonary artery and left atrial pressure divided by blood flow. Nonetheless, it must be remembered that PVR is not a complete description either of the pressure-flow properties (resistance) of the system (West 1985), or of opposition to RV ejection.

The mean drop in pressure from pulmonary artery to left atrium is only 10 mmHg. This is very small compared to the 100 mm Hg pressure gradient across the systemic circulation. However the average amount of blood flowing through both systems over a measured period of time is the same. The systemic circulation needs to pump blood to organs that are far above the level of the heart; this necessitates a higher pressure generation (West 1985). One reason that pressure can be kept at a lower level in the pulmonary vascular system is that the blood has to be pumped is only the height (30 cm) of the lung (West 1985). Thus, the resistance (pressure-flow relationship) of the pulmonary circulation is about one tenth that of the systemic circulation. Resting PVR[#] is reported to range from 56 +/- 24 (Zapol 1982), 100 (West 1985) to 150 +/- 30 dynes.seconds.cm^{-5}. SVR is considerably greater at 1100 +/- 140 dynes.seconds.cm^{-5} (West 1985; Milnor 1982).

What is also remarkable is that the pulmonary vascular resistance has been reported to decrease as pressure and flow in the pulmonary circulation increases (Lake 1990; Nunn 1988; West 1985). As the cardiac output and therefore the pulmonary blood flow increase from resting values of 5 litres per minute to 20 litres per minute, there is a only small rise in pulmonary artery pressure (Lake 1990; Nunn 1988). The pulmonary vascular resistance decreases concomitantly with this increase in flow. Using Poiseuille's formula, this decrease in resistance implies an increase in the radius of the pulmonary vessels. (Figure 1.4.2.1.2) (Lake 1990; Nunn 1988).

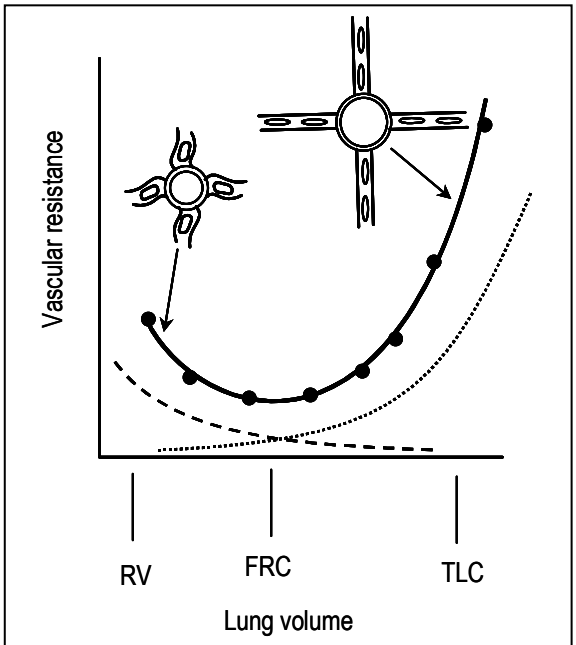


Figure 1.4.2.1.3. The effect of lung volume when the transmural pressure of the capillaries is held constant. At low lung volumes resistance is high as the extra-alveolar vessels are not stretched open and at high volumes, narrowing of the capillaries occur. Pulmonary vascular resistance is lowest at functional residual capacity.
Adapted from West, 1985 and Lake, 1990

The mechanisms by which this decrease in PVR occurs are suggested to be recruitment and dilation of pulmonary capillaries (Figure 1.4.2.1.2) (Lake 1990; Nunn 1988). Under normal circumstances, not all capillaries have blood

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If pressure is expressed in units of dynes per cm^2, and flow as cm^3 per second, then from equation 2.7, the units for vascular resistance are dynes.sec.cm^{-5}; the units mmHg.litre^{-1} minute^{-1} are also used to represent resistance and may be multiplied by a factor of approximately 80 to get dynes.sec.cm^{-5}.

flowing through them. Recruitment is the first process to occur. It refers to the commencement of blood flow via certain capillaries as pressure and flow increase. Dilatation occurs at a later stage. It is a consequence of the pulmonary vasculature being thin walled without much musculature (West 1985).

The site of the greatest pressure drop in the systemic circulation is at the level of the arterioles. In the pulmonary circulation, the pressure drop along the arterioles is relatively smaller than that in the systemic circulation and the site of resistance is equally divided between arterioles, capillaries, and veins. Half of the PVR is situated in the vessels of the pulmonary microcirculation (i.e. vessels that do not have musculature in their walls) that cannot actively contract or dilate (Nunn 1988).

The vascular resistance (radius) of the pulmonary capillaries is determined by their transmural pressure gradient. The transmural pressure gradient is the difference between the intravascular capillary pressure and the pressure in the adjacent alveolus (Nunn 1988; West 1985). Under the influence of gravity, pulmonary artery pressure increases from the top to the bottom of the lung. However, intra-alveolar pressure, at the end of expiration, stays the same from the top to the bottom of the lung. Thus, the transmural pressure gradient, vascular resistance of the alveolar capillaries and blood flow changes from the bottom to the top of the lung (West 1985). When alveolar pressure exceeds the intravascular pressure, capillary size decreases, and resistance increases. This is termed West zone 1. In this zone, the alveolar capillaries are compressed by alveolar pressure, and no blood flow occurs (Figure 1.4.2.1.1). This zone does not occur under normal conditions, as the pulmonary arterial pressure is usually sufficient to raise blood to the top of the lung (West 1985). However, if alveolar pressures increase relative to pulmonary arterial pressure (e.g. IPPV, PEEP, or decreased blood volume), this zone may be present (Nunn 1988; West 1985).

With progression down the lung, West zone 2 occurs. This is where pulmonary artery pressure exceeds alveolar pressure. However, venous pressure is still lower than alveolar pressure. The downstream pressure resisting flow is therefore alveolar pressure and not the distal venous pressure (Nunn 1988; West 1985). The behaviour of such a system where the distal pressure does not play a role in determining resistance is described by a vascular waterfall or weir (Figure 1.4.2.1.1) (Nunn 1988; West 1985). West zone 2 is the predominant area of the lung where recruitment occurs when the critical opening pressure of the vessels is exceeded (Nunn 1988; West 1985).

In West zone 3, the downstream pressure is higher than the alveolar pressure and the alveolar capillaries are kept dilated by the downstream pressure (Nunn 1988). Flow and resistance are therefore determined by the arterial-venous pressure difference and the calculation of resistance by dividing pressure by flow may legitimately be applied in this zone (Nunn 1988).

A fourth zone at the most dependent part of the lung also exists (Nunn 1988; West 1985; West, Dollery et al. 1965). It is a zone of reduced flow due to the compression of the extra-alveolar vessels where the lung is poorly expanded and is more pronounced at small lung volumes (Nunn 1988; West 1985).

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Pulmonary vasoconstriction	Pulmonary vasodilatation
Alpha adrenoreceptor agonists (noradrenaline, adrenaline, and dopamine)	Beta adrenoreceptor agonists
Acetylcholine	Parasympathetic innervation, acetylcholine (weak influence)
Histamine type one receptor agonists	Histamine type two receptor agonists
Bradykinin	Bradykinin
Serotonin	
Angiotensin 2	
Vasopressin	Vasopressin
Prostaglandins: PGH_2, PGF_2 alpha, PGD_2, PGE_2, TXA_2 (thromboxane)	Prostaglandins: PGE_1 and PGE_2 (prostacyclin)
Leucotrines: LTC_4, LTE_4, LTD_4	Adenosine
Platelet activating factor	Atrial natriuretic factor
Adenosine triphosphate	
Low pH, excess of hydrogen ions, carbon dioxide	Higher pH
Potassium ions	
	Nitric oxide

Table 1.4.2.1.1 Effects of vasoactive mediators on pulmonary vascular tone. Adapted from (Nunn 1988; McMurtry, Rodman et al. 1988; West 1985).

The mechanism is analogous to the narrowing of a rubber pipe that occurs when stretched. This narrowing of the alveolar capillaries is the factor dominating PVR at high lung volumes (Figure 1.4.2.1.3) (West 1985).Lung volume also affects pulmonary vascular resistance at the level of the extra-alveolar vessels. Extra-alveolar vessels are pulled open by the radial traction of the lung parenchyma and their resistance decreases at large lung volumes (West 1985). However, the smooth muscle and elastic tissue in their walls tend to collapse these vessels and increase their resistance at low lung volumes (West 1985).

The pressure at which flow commences in the pulmonary vasculature is termed the pressure at zero flow or the critical opening pressure (Lake 1990; Nunn 1988; West 1985). At low lung volumes, when certain extra-alveolar vessels are completely collapsed, a higher than normal intravascular pressure needs to be presented to these

vessels before flow commences (West 1985). In the lung, critical closure can occur at many sites including alveolar, extra-alveolar vessels or pulmonary arterioles (Lake 1990). When critical pressure is considered, the formula for PVR is the quotient of the difference between mean pulmonary artery pressure and critical opening pressure, and cardiac output.

Autonomic nervous system influences on PVR exist. The sympathetic nervous system innervates arterial vessels with a diameter of more than 30 microns. These vessels possesses and beta-adrenergic receptors that, when stimulated, result in vasoconstriction and vasodilatation respectively, (Nunn 1988). Maximal alpha-adrenergic stimulation causes a 25% increase in PVR (Kadowitz and Hyman 1973). Active vasoconstriction and vasodilatation of smooth muscle in the pulmonary vasculature may occur in response to various mediators and stimuli (Table 1.4.2.1.1). However, vasoconstriction is only possible in approximately half the pulmonary vasculature, and is quantitatively and qualitatively is limited and does not have the same powerful effects as in the systemic circulation (Nunn 1988; McMurtry, Rodman et al. 1988)(Nunn 1988; Nimbkar and O'Neill 1973).

It is important to note the following about vasomotion in the pulmonary vasculature:

- The vasoconstrictor phenomena are influenced by lung volume and become more pronounced at low lung volumes (West 1985).
- Both vasodilatation and constriction are caused by the same mediator depending on the route, dose and pre-existing tone of the pulmonary vasculature (McMurtry, Rodman et al. 1988).
- Nitric oxide has been suggested to play an important role in maintenance of normal pulmonary vascular resistance. Its release is impaired in the presence of hypoxia (Johns 1991; McMurtry, Rodman et al. 1988). Other substances, such as prostacyclin, may also have a role to play in the maintenance of the normal low pulmonary vascular tone (McMurtry, Rodman et al. 1988).

Hematocrit %	Average PVR
25	216
33	268
44	375

Table 1.4.2.1.2. PVR changes with changes in hematocrit. Tyson and Fender, 1975

Hypoxic pulmonary vasoconstriction (HPV) is initiated when alveolar partial pressures of oxygen are less than 70 mmHg. HPV is accentuated by a low mixed venous oxygen tension and a low pH (Nunn 1988; West 1985). The physiological response is due to decrease in partial pressures of oxygen in the vessels less than 1 mm in diameter (Nunn 1988). HPV is a powerful physiological phenomenon and can redirect blood flow away from hypoxic areas of the lung. This phenomenon is clinically important as it preserves ventilation perfusion ratios (Nunn 1988).

pH of the blood affects pulmonary vascular resistance and minimal PVR is found at pH of 7.6 (Hosking and Beynen 1992; Lake 1990).

Viscosity directly influences pulmonary vascular resistance. As hematocrit increases, a pari passu increase in PVR occurs. This is in keeping with Poiseuille's law in which viscosity is a factor in the generation of pressure needed to generate a certain flow rate (Tyson and Fender 1975).

1.4.2.2 The use of pulmonary vascular resistance[#] as an index of right ventricular afterload

As discussed, the use of vascular resistance as an indicator of the physical properties of a vascular system and of ventricular afterload is commonplace in medicine. There are similarities in the responses of isolated muscle preparations to increases in afterload, and the decrease in stroke volume in intact right ventricles facing an increase in PVR. Nonetheless, it has been stated that caution should be applied especially when PVR is used to describe characteristics either of the pulmonary vasculature or of right ventricular afterload (Skimming, Cassin et al. 1997; Morpurgo 1995; Lang, Borow et al. 1986; McGregor and Sniderman 1985; Versprille 1984; Mitzner 1983; Milnor 1982b):

1. Pulmonary vascular resistance may not be an accurate expression of the physical properties of the system opposing flow. As the length of blood vessels is constant and viscosity of blood does not ordinarily change, the variable that resistance represents is mainly vessel diameter. If peripheral resistance changes, then it is safe to conclude that vessel diameter of at least some of the vessels in the vascular bed being studied has changed, but this does not necessarily adequately describe the afterload of the ventricle (Lang, Borow et al. 1986). However, PVR has been shown to have little correlation with the change in diameter in the pulmonary capillaries (Morpurgo 1995).

2. Poiseuille's formula describes the ohmic resistance characteristics of steady laminar flow of a "Newtonian" fluid in a rigid cylindrical tube quite accurately (Hilgenberg 1983). The limitations when studying pulsatile flow in living organisms using Poiseuille's formula are apparent as it assumes that:
   i. The flow is constant. It does not address the phasic or pulsatile nature of the circulation (Hilgenberg 1983; Milnor 1982b);
   ii. That blood behaves a Newtonian fluid, which it does not (Versprille 1984; Milnor 1982b);
   iii. The flow pattern is always laminar (Lang, Borow et al. 1986) and that,
   iv. The pulmonary vessels are rigid (Morpurgo 1995).

3. Vascular resistance demonstrates poor correlation with other indices of afterload. Lang et al. (Lang, Borow et al. 1986) have compared SVR and wall stress as indicators of afterload. They demonstrated that SVR is a poor indicator of afterload as compared to wall stress. No literature correlating PVR and right ventricular

[#] Resistance is considered as the opposition to steady flow whereas impedance is the opposition to pulsatile flow in the human cardiovascular system. Resistance is one of the components of impedance.

wall stress could be found.

In patients with pulmonary hypertension, (e.g. mitral stenosis or acute lung injury), PVR has been found to be normal; even though advanced pulmonary hypertension existed (Sandler and Dodge 1963). It has been shown that impedance of the pulmonary circulation changes long before PVR changes: it has been suggested that impedance is a more sensitive indicator of opposition to flow in the pulmonary vasculature (Morpurgo 1995).

4. Resistance as commonly calculated could appear to change due to artefacts in calculation. Consider the pressure-flow curve of a system in which in which flow is laminar and the tube is non-distensible (i.e. it complies with the criteria necessary to apply Poiseuille's formula). *Resistance* to flow is constant, and the *graph of pressure versus flow* for this system will therefore describe a straight line (Figure 1.4.2.2.3 lines a and b) (McGregor and Sniderman 1985; Mitzner 1983). The gradient of this line represents the ratio of pressure to flow i.e. resistance. The resistance in this system remains constant, even if changes in flow and pressure occur (McGregor and Sniderman 1985). A steep gradient implies high resistance and a shallow slope indicates low resistance (Figure 1.4.2.2.3 lines a or b) (McGregor and Sniderman 1985).

However, in a system in which the walls are not rigid but compliant like a real vessel, radius will increase (dilatation) with increasing pressure (McGregor and Sniderman 1985; Mitzner 1983). Therefore resistance will decrease as pressure increases (McGregor and Sniderman 1985; Mitzner 1983). The graph of pressure versus flow will no longer be linear but the slope will decrease with increases in pressure (Figure 1.4.2.2.3 line c). When the limits of the elasticity of the vessel are reached, the pressure flow relationship will again become linear. Most textbooks conclude from this "as flow increases, pulmonary vascular resistance decreases" (McGregor and Sniderman 1985; Mitzner 1983).

However, the evidence available indicates that the slope of the pressure flow curve in the pulmonary vasculature is approximately linear with resistance being constant as flow and pressure change! (Figure 1.4.2.2.3 lines e and e1) (McGregor and Sniderman 1985; Mitzner 1983). A decreasing resistance can therefore not be used to explain the absence of pulmonary hypertension at an increased cardiac output in normal subjects. The conclusion in the preceding paragraph therefore needs to be needs to be carefully considered (McGregor and Sniderman 1985).

An important factor that must be taken into account is that calculation of pulmonary vascular resistance differs for the various West zones (Gilbert, Hessler et al. 1972). The outflow pressure (P_2 in equation 1.4.2.4) in the PVR calculation is considered to be equivalent to left atrial pressure. This is indeed true for West zone 3 conditions, where the vessels are held widely open and the venous pressure is the pressure opposing flow. Calculations of resistance across the lung at this (Poiseuille's) zone may legitimately use LAP as an accurate reflection of downstream pressure (Versprille 1984; Gilbert, Hessler et al. 1972).

However, much of the normal lung vasculature falls in West zone 2 where resistance is determined by the forces that occur in a Starling resistor (Figure 1.4.2.1.1) (Versprille 1984; Mitzner 1983; Gilbert, Hessler et al. 1972). If we

consider Equation 1.4.2.4, [($P_1 - P_2$) / Q = R], the driving pressure, P_1 is as is usual for the pulmonary circuit, mean pulmonary artery pressure. The outflow or downstream pressure of the circuit does not however play a role in the resistance of such a circuit (Mitzner 1983; Gilbert, Hessler et al. 1972). The distal pressure, P_2, in the calculation of PVR, is therefore the pressure tending to collapse the Starling resistor ($P_{STARLING}$).

When pulmonary artery pressure (P_1) is less than $P_{STARLING}$, no flow will occur (West zone 1). When P_1 exceeds P_s, the vessel opens and flow commences (Mitzner 1983). This is seen in Figure 1.4.2.2.3 as the pressure intercept of lines e and e1 not passing through the origin, but at a pressure equal to $P_{STARLING}$. The pressure intercept ($P_{STARLING}$) at which flow first occurs is called the critical opening pressure (McGregor and Sniderman 1985; Mitzner 1983). The calculation of resistance for these zones where Starling resistors exist should use critical opening pressure as the downstream pressure (McGregor and Sniderman 1985). It must also be remembered that the resistance described by the equation 1.4.2.4 is the resistance upstream of the critical opening pressure and does not describe trans-pulmonary resistance (Gilbert, Hessler et al. 1972).

What happens if the critical pressure is ignored or not known and LAP is used as the downstream pressure? The pressure versus flow plot will still be linear, albeit the slope will be altered (Figure 1.4.2.2.3 f_1, f_2, and f_3) (McGregor and Sniderman 1985; Mitzner 1983). This will however lead to the following interesting artefact: the resistance (P/Q) versus flow plot will decrease as the flow increases (Figures 1.4.2.2.3 d and 1.4.2.2.4 top) (McGregor and Sniderman 1985). This error is greater in patients with a high critical opening pressure (McGregor and Sniderman 1985). This may lead to incorrect conclusions being made about the nature of the pulmonary bed i.e. that PVR decreases as flow increases.

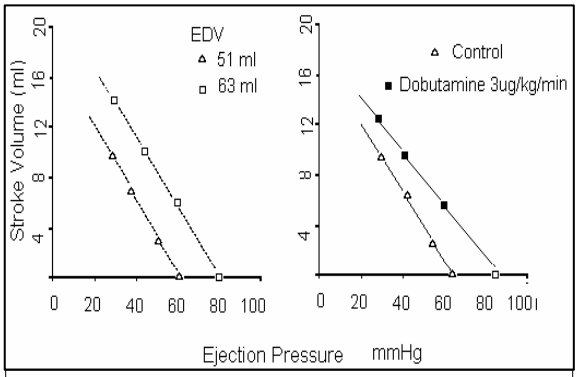


Figure 1.4.2.2.1. Right ventricular stroke volume is determined by ejection pressure, end-diastolic volume (EDV) and contractile state. In the left panel, EDV's of 51 and 63 ml representing filling pressures of 5 ad 10 mmHg for the normal canine right ventricle. For either filling volume an inverse relationship exists between stroke volume and ejection pressure. The ventricle with the larger EDV was able to eject a larger stroke volume for any given ejection pressure. In the right hand diagram, the filling pressure was kept constant. An increase in contractility mediated by dobutamine resulted in a bigger stroke volume for any ejection pressure. Adapted from Weber, Janicki et al, 1983

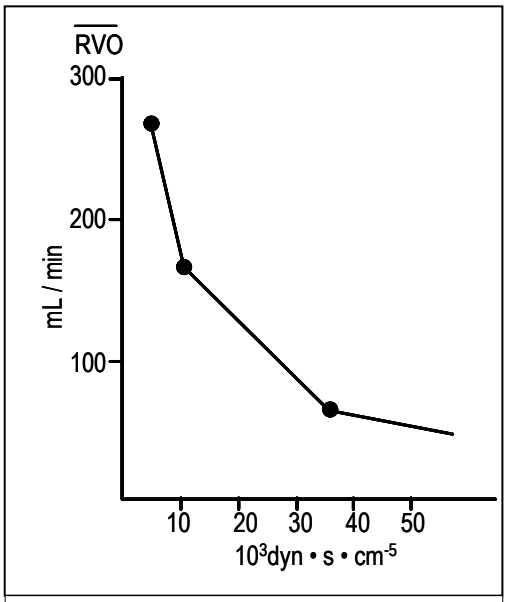


Figure 1.4.2.2.2. Outflow from the right ventricle decreases as the resistance of the pulmonary circulation increases.

Adapted from Piene and Sund, 1979

In summary, the practice of using LAP instead of critical opening pressure in the calculation of resistance in Zone 2 can at times lead to false interpretation of data. The ratio of "(mean pulmonary artery pressure – LAP) / flow" will change as flow changes without their being any change in the forces opposing flow (Figure 1.4.2.2.3 f) (McGregor and Sniderman 1985; Versprille 1984). A manoeuvre causing an increase in cardiac output without rises in pressure would therefore seem to have induced vasodilatation (McGregor and Sniderman 1985; Versprille 1984). Vasodilatation can only be deemed to have taken place when the slope of the P/Q relationship becomes less steep, i.e. when pressure decreases or stays unchanged in the face of an increase in flow (McGregor and Sniderman 1985). If however, West zone 3 conditions exist where the distal (LA) pressure is the true downstream pressure, then accurate reflections of the opposition to pulmonary flow will be attained. In other words, the true slope of the pressure-flow relationship (the true PVR) will be calculated.

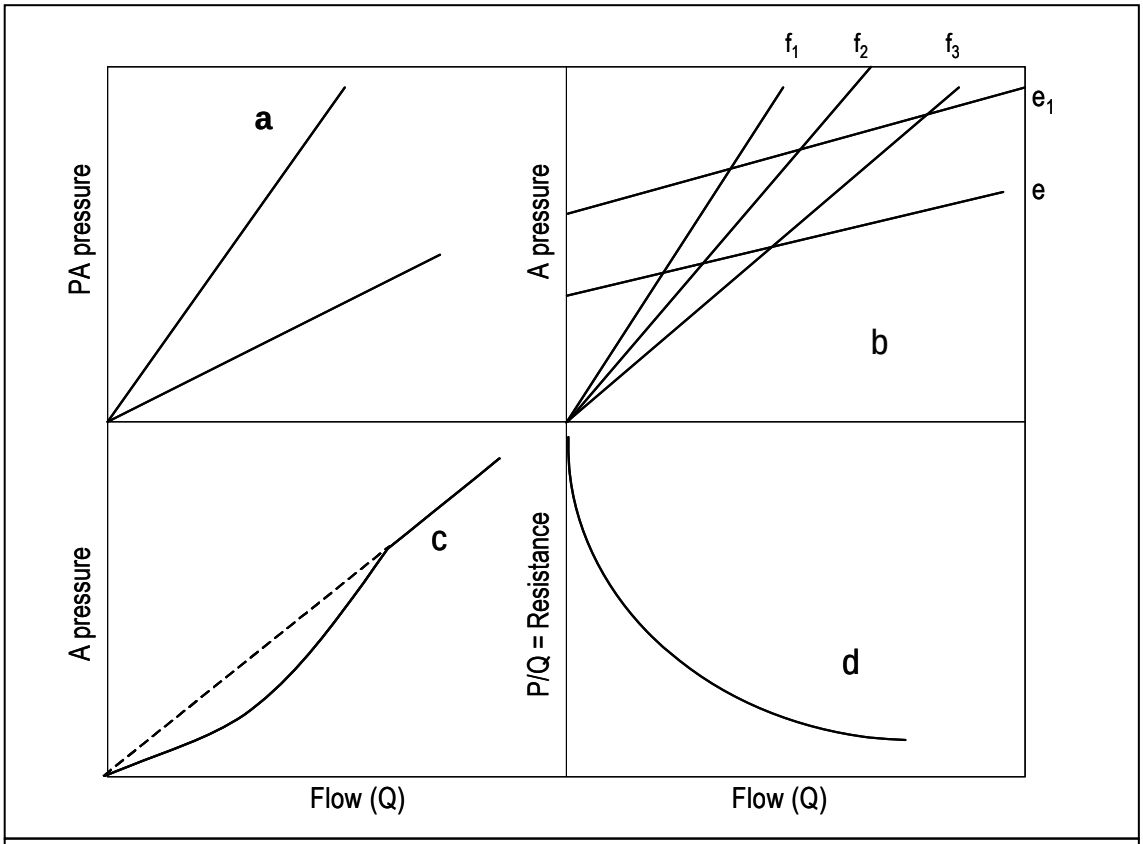


Figure 1.4.2.2.3. See text for details. Adapted from Alvarez, Casa et al. 1990.

The slope of the true pressure-flow relationship in the lung is approximately 1.6 mmHg.litre^{-1}.min^{-1}.m^{-2}, or 3.3 mmHg.litre^{-1}.min^{-1}.m^{-2} per lung (West 1985). Thus, the normal lung has a low resistance to flow and this will explain the very small increase in pressure as flow increases.

Extrapolation of the pressure-flow relationship back to the point at which flow first commences allows us to determine the critical opening pressure which is widely considered to be in the order of 5 to 10 mmHg in the normal human lung (McGregor and Sniderman 1985; Lodato, Michael et al. 1985). Both the slope of the pressure-flow relationship and the critical opening pressure should be included as part of the description of PVR (Figure 1.4.2.2.3, lines e_1 and e_2) (Versprille 1984).

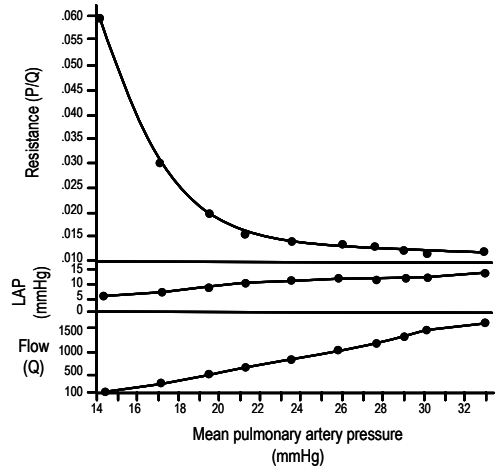


Figure 1.4.2.2.4

Top: resistance versus mean pulmonary artery pressure graph.

Middle: LAP versus mean pulmonary artery pressure

Bottom: Flow versus pressure relationship.

True resistance (slope of the bottom flow versus pressure graph) is constant, but "resistance" as represented by the pressure-flow versus pressure relationship falls steeply as pulmonary artery pressure increases.

McGregor and Sniderman, 1985

A true increase in resistance, elevation of critical opening pressure or LAP should all be considered in the generation of pulmonary hypertension. Depending on which mechanism is operative, there will be a difference in how the pressure responds to an increase in cardiac output. Therefore if the cause of pulmonary hypertension is due to:

1. A true increase in resistance, any increase in flow will result in an increase in pressure (Figure 1.4.2.2.3, lines a and b) or,
2. An increase in critical opening pressure, pulmonary flow could almost double before any significant increase in pressure occurred (Compare lines e_1 and e in Figure 1.4.2.2.3) (McGregor and Sniderman 1985).

What is quantitatively known about critical opening pressure and pulmonary vascular resistance in patients with various causes of pulmonary hypertension is summarized in Table 1.4.2.1 below.

Pathophysiology	Resistance	Critical Opening Pressure
Normal	1.6 mmHg.litre^{-1}.min^{-1}.m^{-2}	10 - 12 mmHg
Chronic obstructive airways disease	Normal	> 30 mmHg
Mitral stenosis	Normal	> 20 mmHg
Left heart disease	Increased	44 mmHg
True increased PVR	Increased	Increased

Table 1.4.2.1 Critical opening pressure and PVR in various pathophysiological states

1.4.3 Pulmonary vascular impedance

The heart is a pulsatile pump that generates repetitive changes in blood flow, pressure and afterload. Between one half to one third of the hydraulic power produced by the right ventricle is needed solely to generate the pulsatile

components of flow (Grant and Lieber 1996; Piene and Hauge 1976). Vascular resistance expresses opposition to steady flow, and is not a comprehensive description of the opposition to pulsatile flow (Morpurgo 1995). The factors that oppose pulsatile flow are best described in terms of vascular impedance (Morpurgo 1995; Milnor 1982). The concept of impedance has been borrowed from electrical engineering. This concept is analogous to the impedance concept that is used to describe the relationship between voltage and current in alternating current circuits (Fourie, Coetzee et al. 1992; Fourie, Coetzee et al. 1992a; Milnor 1982c).

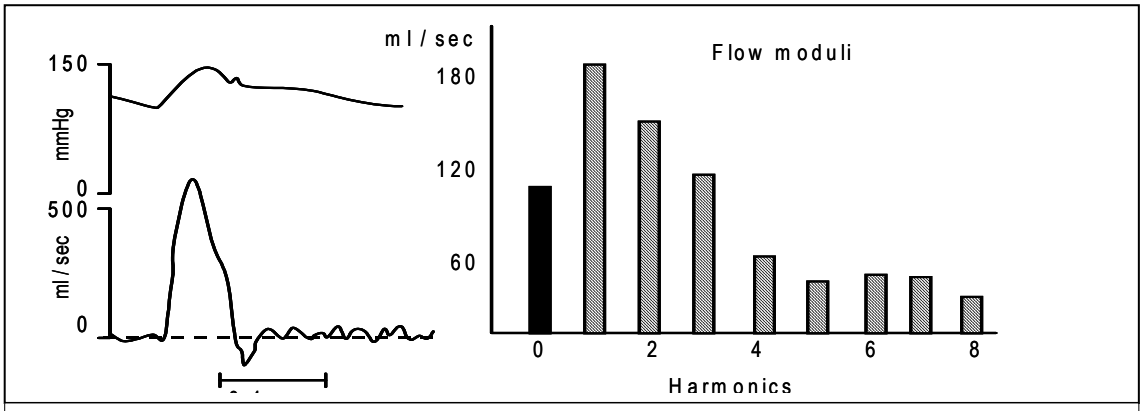


Figure 1.4.3.1. A Fourier analysis illustrating the harmonics of the flow curve in the aorta. Nichols, Conti et al, 1977

Consecutive branches of the vascular bed differ in their dimensions and elasticity. These branches are responsible for the generation of reflected pressure and flow waves (Morpurgo 1995; Hijazi and Hellenbrand 1992; Bergel and Milnor 1965). Thus, both flow and pressure measured in the main pulmonary arteries are composed of a mixture of the incident and reflected waves. When the forward pressure waves collide with pressure waves reflected backward from the bifurcations, the proximal pressure increases. (This is assuming that both are positive waves at the point of incidence). However, summation of the incident and reflected waves decreases the proximal flow rate. This creates a lag between the peak of the flow and pressure waves and they become out of phase with each other. The phase difference between flow and pressure is a part of the usual description of vascular impedance.

Input impedance ($Z_{in}(\omega)$) expresses the opposition of the vascular system to pulsatile flow at a particular vascular cross section. As the waves reflected from distal sites in the vasculature vary from point to point in a vascular bed, input impedance is specific to a particular vascular cross section and the vasculature distal to it. Input impedance incorporates all the factors that oppose flow in that particular (pulmonary) vascular bed (Milnor 1982). Theses factors can be divided into the following:

1. Factors related to the properties of the fluid being moved, being
   a. The inertia and,
   b. Viscosity of blood and,
2. Factors related to the vasculature, being:
   a. The resistance presented by the pulmonary vasculature,
   b. The compliance of the pulmonary arteries, and the
   c. Waves reflected from the peripheral vessels.

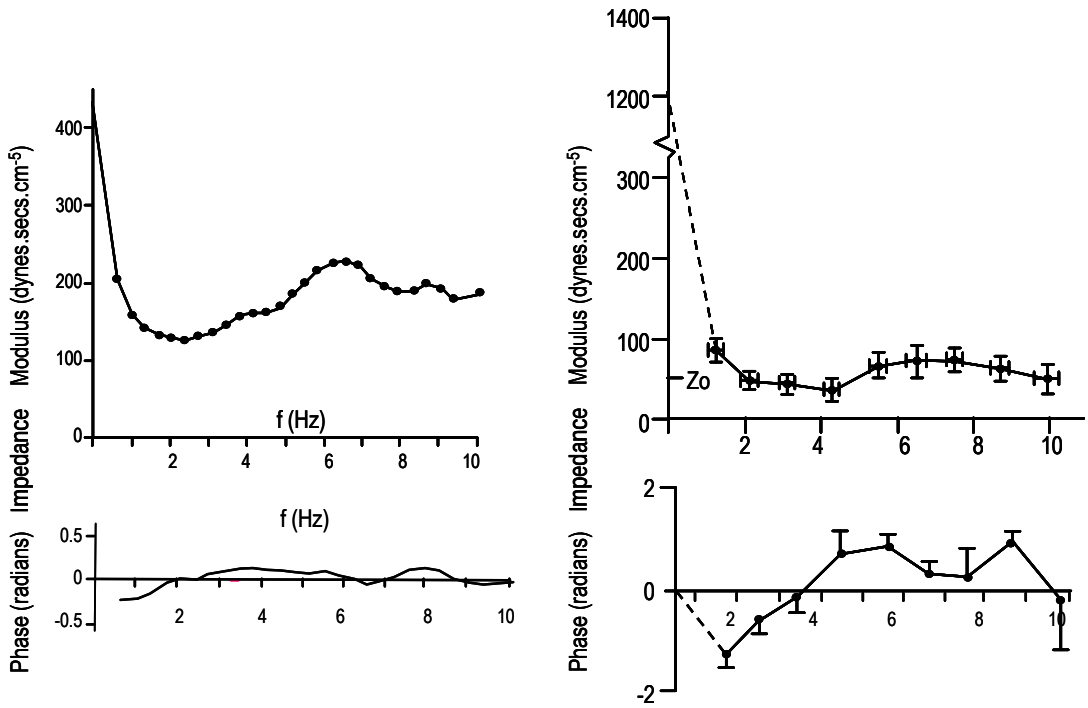


Figure 1.4.3.2. Input impedance spectra measured in A: the canine pulmonary artery (Milnor 1982) and B: the human aorta (Nichols 1977). (No input impedance spectrum of a human pulmonary artery could be found). The units on the y-axis are dynes.seconds.centimetres^{-5} and the x-axis units are frequency in hertz. The bottom graphs indicate the phase changes that occur as the frequency changes. Note that at high frequencies, input impedance approximates characteristic impedance and that at zero frequency, impedance approximates peripheral arterial resistance. These diagrams were reproduced in Milnor, 1982c. The aortic impedance spectrum was originally published by Nichols et al 1977.

It is insightful to understand how input impedance is measured. Accurate measurements of instantaneous flow and pressure are made just beyond the aortic or pulmonary valves (Equation 1.4.3.1) (Thys and Dauchot 1998). These measurements are then subjected to Fourier analysis: this process identifies the sinusoidal waves that comprise the harmonics of flow and pressure of each arterial pulse wave (Figure 1.4.3.1) (Piene 1986). The ratio of the corresponding pressure and flow wave amplitudes are then calculated.

$$Zin(\omega) = P(\omega) / Q(\omega) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.3.1}$$

Where

$Zin(\omega)$ = input impedance modulus

$P(\omega)$ = pressure modulus

$Q(\omega)$ = flow modulus, and

(ω) indicates the phases of the pressure and flow waves.

These amplitude ratios *and* the associated phase shift values are plotted against frequency to create an input impedance spectrum (Figure 1.4.3.2) (Thys and Dauchot 1998; Parbrook, Davis et al. 1985). Input impedance cannot therefore be expressed as a single number as can resistance, but rather as two sets of numbers. The first is

the graph of impedance modulus[#] versus frequency, and the second, a graph of phase versus frequency (Grant and Lieber 1996). The frequencies over which impedance is measured is typically up to 12 or even 25 Hertz: values above this are usually excluded as they represent noise in measuring systems (Milnor 1982c; Nichols, Conti et al. 1977). The units of both input impedance and vascular resistance are dynes.seconds.centimetres^{-5}.

At zero frequency the modulus of input impedance is maximal and the phase is zero (Z(0)) (Piene 1986). Conceptually, at constant flow, the modulus of input impedance in a three-element Windkessel model is determined by the sum of Zc and Rp, as compliance will be constant at a particular flow rate. Z(0) can be approximated from mean pressure divided by mean flow.

$$Z(0) = MAP/CO \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.3.2 (Fourie, Coetzee et al. 1992)}$$

If the distal vascular bed were a continuation of the proximal vessel with the same physical properties (i.e. if the vasculature were a uniform tube), no reflected waves would be present. The opposition to flow under such circumstances would be called the characteristic impedance (Zc or Rc) and would not be different from input impedance (Zin(ω)) (Fourie 1989; Fitzpatrick and Grant 1989). Under normal circumstances, the relationship between the two is such that the input impedance spectrum (Zin(ω)) oscillates around the numerical value of the characteristic impedance (Zc) because of waves reflected from the periphery (Figure 1.4.3.2) (Grant and Lieber 1996; Morpurgo 1995; Milnor 1982c; Nichols, Conti et al. 1977; Nichols, Conti et al. 1977)

Because of oscillations caused by waves reflected from the periphery, characteristic impedance cannot be measured in vivo but has to be estimated by averaging impedance moduli that occur over a range of frequencies. Wave reflection is minimal at higher frequencies due to attenuation by the vessel wall (Grant and Lieber 1996). As a result, the pressure and flow are in phase. Therefore the phase shift is close to zero and characteristic impedance (Zc) can be represented by a single number (Grant and Lieber 1996). The steep portion of the input impedance spectrum (Zin(ϖ)) that occurs at lower frequencies is therefore omitted when calculating Zc. The frequencies used to calculate characteristic impedance should be specified, for example 'characteristic impedance (Zc) which is calculated between 8 and 18 hertz for the pulmonary circulation, is…' (Milnor 1982c; Nichols, Conti et al. 1977).

Womersley's equation for characteristic impedance is instructive (Piene and Hauge 1976):

$$Zc = \rho c_0/\sqrt{(1 - \sigma^2)} \times 1/ (M_{10} \times e^{-j\varepsilon 10}) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.3.3}$$

Where

[#] The use of complex numbers and the term "modulus" is discussed briefly in the appendix of this document.

Note that the term "modulus" refers to the absolute value of input impedance (frequency dependent ratios of pressure to flow). An increase in the modulus of the input impedance refers to an increase in the absolute value of the ratio of pressure to flow at a particular frequency or frequencies. In older (Bergel and Milnor 1965) and the more recent literature (Lowe, Hettrick et al. 1996; Hettrick, Pagel et al. 1995), the term "modulus" has been omitted and the term "magnitude" used instead when describing the absolute value of impedance.

ρ is density of the fluid

c_o is wave velocity

j is $\sqrt{-1}$

σ is the Poisson ratio

and the parameters M and ε_{10} are dependent on viscosity, density, frequency and vessel radius.

Therefore characteristic impedance (Zc), like input impedance, depends on the physical properties of the vessel, the fluid it is conducting, and the velocity of the fluid. Characteristic impedance (Zc) varies directly with the elasticity and indirectly with the compliance of the vessel and inversely with its cross-sectional area. This means that the stiffer the tube and the smaller its radius, the higher the characteristic impedance will be (Milnor 1982c; Piene and Hauge 1976).

In models that were developed to represent the pulmonary circulation, Milnor has shown that the characteristic impedance (Zc) declines slightly in the first few branches of the pulmonary artery and then rises 10% per generation until the pulmonary capillaries are reached. The initial drop in Zc is probably due to the increase in cross sectional area that occurs as the capillaries are approached (Milnor 1982c).

The pulmonary input impedance spectrum (Zin(ϖ)) in both humans and animals typically falls steeply from a high value at zero hertz to a minimum at 2 to 6 hertz (Hijazi and Hellenbrand 1992; Piene 1986; Bergel and Milnor 1965; Milnor 1982c). The exact value at which the impedance minima occur varies with the animal species studied (Figure 1.4.3.2) (Piene 1986; Milnor 1982c).

An interesting aspect of the input impedance is the phase versus frequency plot (Figure 1.4.3.2). The plot of phase against frequency shows an initial negative phase: this indicates that, under normal circumstances, flow leads pressure. Therefore at lower (physiological) heart rates, the high compliance of the pulmonary vessels allows blood to be ejected into the vasculature with little initial rise in pressure (Fourie, Coetzee et al. 1992; Fourie 1989; Piene 1986; Bergel and Milnor 1965). The positive phase evident at higher frequencies indicates that pressure leads flow due to the inertia of blood (Figure 1.4.3.2 and Figure 1.4.3.2.1) (Fourie, Coetzee et al. 1992; Piene 1986; Milnor 1982c; Randall and Stacy 1956).

Caro and McDonald conducted the first study of pulmonary input impedance in isolated rabbit lungs (Hijazi and Hellenbrand 1992). Later studies, such as the classic one by Bergel and Milnor confirmed and extended this work by including the phase difference between corresponding harmonics of pressure and flow in their studies (Bergel and Milnor 1965). Pulmonary vascular input impedance has been infrequently studied in humans due to technical demands and its study necessitating the placement of invasive measuring devices. Milnor and colleagues however successfully studied pulmonary artery input impedance during cardiac catheterisation in humans being investigated for mitral stenosis (Milnor, Conti et al. 1969) and a close correlation was found with animal studies (Hijazi and Hellenbrand 1992; Bergel and Milnor 1965; Pouleur, Lefevre et al. 1978; Piene and Hauge 1976; Reuben, Swadling et al. 1971).

1.4.3.1 Windkessel models used in describing impedance

Since impedance is difficult to measure in vivo, it is conceptually convenient to visualize the vascular system in terms of an electrical model: this has been an ongoing development since the 19th century (Milnor 1982; Randall and Stacy 1956). The approach has been to create an electrical circuit that has similar impedance to pulmonary arterial input impedance or other vascular beds being studied. To mimic the impedance characteristics of the systemic or pulmonary vascular beds accurately, these so called 'lumped element' models need to incorporate resistive, elastic and inertial elements (Figure 1.4.3.1.1) (Randall and Stacy 1956).

Noordegraaf developed a three-element Windkessel model that has been extensively used to describe the vascular system (Figure 1.4.3.1.1) (Westerhof, Elzinga et al. 1971). The three elements Noordegraaf incorporates are a capacitor and two resistances. The capacitor imitates the elastic behaviour of the arterial tree in which energy can be temporarily 'stored'. The rise in pressure for a particular stroke volume inputted into the vessel also represents a parameter of resistance that the ventricle has to overcome. The resistances represent peripheral resistance (Rp) and characteristic impedance (Zc) (Fourie 1989; Westerhof, Elzinga et al. 1971). This modified three-element Windkessel model has been shown to be able to closely estimate the input impedances of both the PA and aorta when appropriate pressures and flows are incorporated into it (Fourie 1989; Grant and Paradowski 1987; Sunagawa, Maughan et al. 1985; Westerhof, Elzinga et al. 1971).

Various arrangements of the components in a Windkessel model have been systematically studied as to their ability to accurately describe PA input impedance (Grant and Paradowski 1987). Noordegraaf's model may be the one most commonly used, but is by no means the only arrangement that can accurately predict pulmonary input impedance (Grant and Paradowski 1987). In fact, model F in Figure 1.4.3.1.1 better represents pulmonary input impedance than any of the other models tested.

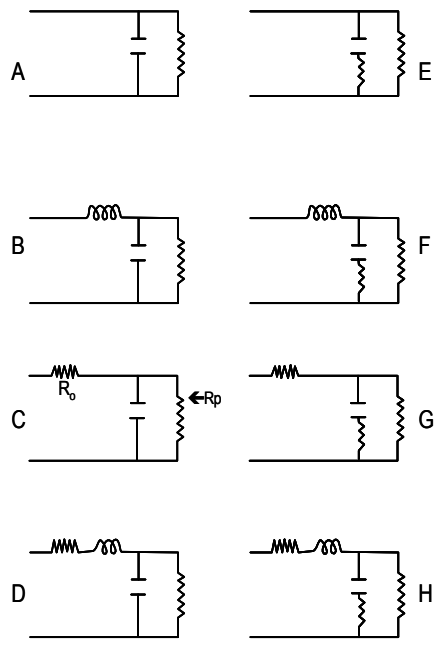


Figure 1.4.3.1.1. 8 'lumped element' electrical analogues that have been tested to compare how they predicted pulmonary arterial input impedance. The models that fitted the Zo of the pulmonary circulation best were models C to F. Redrawn from Grant and Paradowski, 1987

A: Two-element Windkessel model (1899).

B: Inductance added to the two-element model. The inductance represents the inertia of the blood.

C: Westerhof's three-element model (1971) in which the inductance is replaced by a resistor. The resistor Ro represents Rc.

D: A later version of C with an inductor introduced in series with the second resistor.

The modified three-element Windkessel model concept can be described in hydraulic terms that parallel the normal ventricular–arterial interaction as follows. Flow from a phasic pump (the ventricle or AC generator) enters a chamber through a one-way valve (diode), distending the elastic wall (capacitance) of the Windkessel (German for 'air compression chamber'). A resistor is inserted here as it plays an important role in dictating flow at this point. (a simple resistor may be used as frequency plays little or no role in determining characteristic impedance). When the inflow into the chamber stops, the elastic wall recoils and fluid exits the chamber through the resistance of the narrow outflow tube (Rp). The elasticity of the arteries causes a phase shift between the pressure and flow waves (Hettrick, Pagel et al. 1995; Fourie, Coetzee et al. 1992a; Grant and Paradowski 1987; Milnor 1982; Pouleur, Lefevre et al. 1978).

Westerhof subsequently developed and verified the accuracy of a hydrodynamic model of the arterial vasculature that was derived from the earlier electrical model that he developed (Westerhof, Elzinga et al. 1971). The purpose of developing such a model was to utilize it in studies in which the isolated heart pumps into a mock arterial system. A further advantage of this hydrodynamic model is that reflected waves are present. Their presence is an advantage over the electric analogue model (Grant and Lieber 1996). A normal load is therefore presented to the ventricle and a normal arterial pressure (aorta or pulmonary artery) pattern is generated. The hydrodynamic model can then be adjusted to study the effects of changing various parameters such as C, Zc or Rp on the ventricular-vascular interaction (Grant and Paradowski 1987; Milnor 1982). That we need a complex model incorporating resistive, inductive, capacitances and reflective waves emphasizes that a simple resistive device (e.g. a constriction of the artery exiting the relevant ventricle) is inadequate to model the impedance presented by the circulation (Calvin, Jr., Baer et al. 1985; Milnor 1982).

The input impedance spectrum may be mathematically expressed as a function of a 3 element modified Windkessel model (Sagawa, Maughan et al. 1988; Hettrick, Pagel et al. 1995) relatively simply as

$$Zin(\omega) = Zc + ((Rp / (1 + j\omega C\, Rp) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.3.1.1}$$

Where

$Zin(\omega)$ = input impedance at a particular frequency ω,

ω = frequency,

Zc = characteristic impedance,

Rp = peripheral arterial resistance,

C = compliance, and

j = χ-1

The usefulness of the above equation is that it makes clinicians aware that impedance or opposition to flow in the pulmonary vasculature is directly proportional to the sum of Zc and Rp and inversely proportional to the compliance of the system. Frequency and phase angle also play a role in determining impedance.

1.4.3.2 Factors influencing pulmonary vascular impedance

We will explore various factors affecting impedance to blood flow in the pulmonary vascular bed. Changes in impedance can be brought about by three principal mechanisms (Morpurgo 1995):

1. Radius of peripheral vasculature affects the reflection of incident waves and thereby alters the magnitude of the impedance moduli;
2. An increase in cross-sectional area of the large proximal pulmonary arteries decreases characteristic impedance and vice versa, and/or,
3. Change in compliance: a decrease in compliance shifts the minima and maxima of the impedance spectrum to the right.

The pulmonary input impedance spectrum is qualitatively similar in dogs, rabbits, cats and humans. However, as impedance depends on the physical characteristics of the pulmonary bed, moduli of the impedance spectrum at similar frequencies may vary quantitatively between subjects of various sizes (Piene 1986). The similarity in shape of the input impedance spectrum suggests that conclusions drawn from animal studies are applicable to the human pulmonary vasculature (Milnor, Conti et al. 1969). Characteristic impedance falls from 1000 dynes.s.cm^{-5} in rabbit and cat lungs (Hijazi and Hellenbrand 1992; Piene 1986; Piene and Hauge 1976) to 200 dynes.s.cm^{-5} in dogs (Bergel and Milnor 1965; Pouleur, Lefevre et al. 1978; Pouleur, Lefevre et al. 1978) to approximately 30 dynes.s.cm^{-5} in humans (Milnor, Conti et al. 1969). This decrease in characteristic impedance with increases in body size is related to both increasing size and compliance of the larger PA's, and also decreasing peripheral resistance (Piene 1986).

Similar to the species differences in impedance spectra, input impedance spectra in the main pulmonary artery and aorta are qualitatively similar. Not surprisingly, the moduli of impedance at similar frequencies are much lower in the pulmonary artery than the aorta (Figure 1.4.3.2). Typical characteristic impedance in the human pulmonary vasculature is 23 to 30 dynes.seconds.centimetres^{-5} and in the aorta is 74 dynes.seconds.centimetres^{-5} for frequencies above 2 hertz (Piene 1986; Milnor 1982c). As the diameters of the aorta and the pulmonary artery are approximately equal and both carry the same average volume of blood per unit time, this difference may be attributed to a greater compliance of the PA (Piene 1986). Pulmonary vascular resistance is only one fifth of the systemic vascular resistance, but characteristic impedance in the pulmonary circulation is half that in the systemic circulation. The ratio of peripheral resistance to characteristic impedance is two to three times higher in the pulmonary circulation than in the systemic circulation. The implication is that input impedance plays a more important role in the pulmonary than the systemic afterload (Piene 1986). It follows therefore that non-pulsatile work (the product of mean pressure and time averaged flow), accounts for the majority of the energy expenditure of both the left and right ventricles. However, pulsatile flow accounts for 30 to 50% of the energy expended by the right ventricle, but only 15% of that expended by the left ventricle (Figure 1.4.3.2.3) (Morpurgo 1995).

PA input impedance is affected largely by the first five divisions of the pulmonary artery, in decreasing levels of importance. Measurements of input impedance take into account both forward and reflected flow and pressure waves. The reflections are predominantly caused by branching in the vasculature. Different waves will be encountered at different points in the vasculature. Thus, the site at which the measurement of input impedance was made must be specified, as the measurement is specific for a particular site in the vasculature. Typically, measurements of pulmonary vascular impedance are made with a catheter in the main PA and aortic impedance in the ascending aorta. Furthermore, the pulmonary vasculature behaves as if it has a single reflecting site generating

reflected waves that affect input impedance[#]. It is interesting that the main site where reflection occurs can be determined as follows: the physical distance between the site of measurement of impedance and the main site of wave reflection in the peripheral pulmonary vasculature equals one quarter of a wavelength of the frequency at the first impedance minimum (Cohen, Kirschner et al. 1988; Bergel and Milnor 1965; Reuben, Swadling et al. 1971). This site is located in the vessels between the pulmonary arterioles and the capillary bed i.e. in the small (extra-alveolar) arterioles of less than 0.5 to 1 mm in diameter (Hijazi and Hellenbrand 1992; Bergel and Milnor 1965; Piene and Hauge 1976; Milnor, Conti et al. 1969). It is also known that the pulmonary capillaries are the sites of pulmonary vascular resistance (opposition to non-pulsatile or static flow), whereas the proximal PA is the first structure causing opposition to RV output beyond the pulmonary valve and plays a dominant role in determining characteristic impedance (Grant and Lieber 1996). These relationships help to determine the effects of various manoeuvres and drugs on the reflection site in the pulmonary vasculature (Figure 1.4.3.2.5).

Bergel and Milnor originally demonstrated that changes in capillary and arteriolar diameters have differing effects on resistance and impedance (Bergel and Milnor 1965). They studied the effects of lung inflation (up to 20 cm H_2O) on the impedance spectrum. Lung inflation compresses alveolar capillaries but at the same time increases the radius of extra-alveolar vessels. This degree of lung inflation therefore results predominantly in alveolar capillary compression and an increase in pulmonary vascular resistance (Piene 1986). In keeping with these concepts, lung inflation has been consistently demonstrated to produce a significant increase in the input impedance modulus at 0 hertz (i.e. a predominant increase in resistance) (Piene 1986; Bergel and Milnor 1965; Calvin, Jr., Baer et al. 1985; Pouleur, Lefevre et al. 1978). Input impedance spectra above one to two hertz are little affected by alveolar vessel diameter if the pulmonary artery pressure is kept constant (Figure 1.4.3.2.4) (Piene 1986). Other influences on alveolar capillary size, such as compression by PEEP or capillary dilatation by increased left atrial pressure, similarly have little effect on the input impedance spectrum above two hertz (Piene 1986; Bergel and Milnor 1965; Calvin, Jr., Baer et al. 1985; Fitzpatrick and Grant 1989).

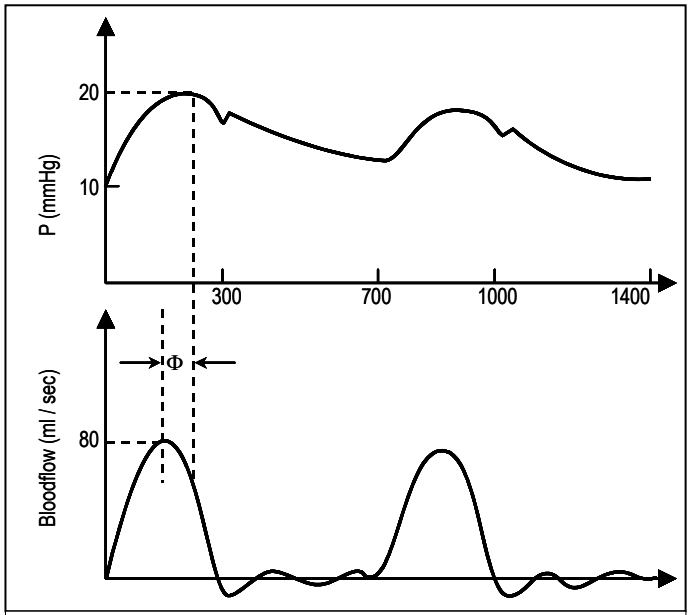


Figure 1.4.3.2.1. The pressure and flow waves generated in the pulmonary artery. Flow leads pressure with a phase angle of ϕ. Fourie, 1989

[#] The distance from the measuring site to reflecting site is a quarter of the wavelength of the frequency at the impedance minimum. Therefore, from $\lambda=f/c$, (where λ is wavelength at a designated frequency, f is frequency at the first impedance minimum, and c is velocity of blood flow which, in the PA, is approximately 200 mm per second), the reflecting site can be anatomically located by the quotient of $\lambda/4$ as a measurement in centimeters from the point of measurement of impedance (Reuben, Swadling et al. 1971).

Apart from the effects on PVR, Bergel and Milnor found evidence of increased wave reflection with increasing airway pressure. Lung inflation caused the moduli of input impedance between 3 to 6 hertz to increase (Figure 1.4.3.2.4) (Bergel and Milnor 1965). They explain their finding in the following way. Wave reflection occurs where the radius of vessel segments changes. During lung inflation, greater reflection of waves is due to an increase in radius of the extra-alveolar vessels, rather than alveolar capillary compression (Piene 1986).

As changes in the capillary bed predominantly affect pulmonary vascular resistance and contributes relatively little to changes in input impedance, it follows that changes of impedance and resistance may be dissociated from one another (Fourie and Coetzee 1993; Piene 1986; Bergel and Milnor 1965; Pouleur, Lefevre et al. 1978; Milnor, Conti et al. 1969). This again emphasizes that PVR describes only one particular aspect of afterload. That mean and pulsatile components of RV output are dependent on different portions of the pulmonary circulation, suggests that they can be controlled separately, and provides a hitherto unexplored therapeutic modality (Grant and Lieber 1996).

Input impedance in the lung vasculature should be measured at similar phases of the respiratory cycle as respiration may significantly affect it (Morpurgo 1995). Early studies however, found no effects of respiration on pulmonary input impedance (Hijazi and Hellenbrand 1992; Bergel and Milnor 1965); this was possibly due to insensitivity of older measuring equipment.

Infusions of serotonin, and alveolar hypoxia produce similar effects on input impedance (Piene 1986; Bergel and Milnor 1965; Piene and Hauge 1976; Reuben, Swadling et al. 1971). The main reflecting site moves to a more proximal position, an increase in the reflection coefficient[#] occurs, and the impedance minima shift to higher frequencies. Alveolar hypoxia increases characteristic impedance (Morpurgo 1995; Piene 1986; Bergel and Milnor 1965; Reuben, Swadling et al. 1971). These observations seen during hypoxia are consistent with the development of generalized pulmonary vasoconstriction (Piene 1986).

Sympathetic stimulation or infusions of adrenaline tend to stiffen the walls of the pulmonary vessels but have little effect on vessel calibre (Piene 1986; Reuben, Swadling et al. 1971). Stiffening of the vessel walls leads to an increase in characteristic impedance, but the associated increase in pulmonary artery pressure and flow tends to dilate the vessels (Piene 1986). Therefore stimulation of the sympathetic nervous system produces competing

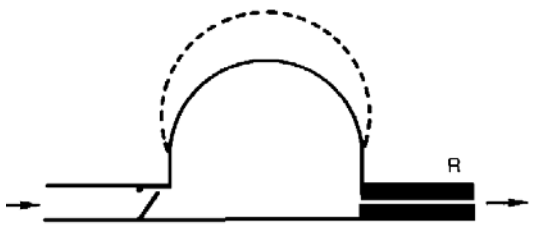


Figure 1.4.3.2.2. A model of a vascular tree to explain the Windkessel models of the circulation. Flow enters the chamber through a one-way valve on the left and distends the elastic wall as shown by the dashed line. When inflow ceases, the wall recoils and the valve closes and fluid leaves through the narrow resistance on the right. The model illustrated here would correspond to model A in Figure 1.4.3.1.1. Redrawn from Milnor, 1982

[#] The reflection coefficient (also termed the arterial wave reflection factor) ($\Delta Z/Zc$) is defined as the ratio of the difference between Zin (ω) at the impedance minimum and the following maximum of Zin(ω), and Zc. This ratio is proportional to the magnitude of reflected waves (Hettrick, Pagel et al. 1995)

effects that limit the impact of an increase in impedance. This again emphasizes the multifactorial nature of factors that determine impedance (Piene 1986).

Fitzpatrick and Grant compared the effects of three forms of vascular obstruction (PEEP, occlusion of the left pulmonary artery and pulmonary embolism) on pulmonary input impedance (Fitzpatrick and Grant 1989). All three manoeuvres increased mean PAP. PEEP produced no changes in characteristic impedance or compliance; occlusion of the left pulmonary artery increased characteristic impedance (24%) and decreased compliance (50%) of the PA.

In Fitzpatrick and Grant's study, one of the factors that were suggested to increase characteristic impedance after pulmonary artery clamping was active vasoconstriction of the main PA (Fitzpatrick and Grant 1989). Fitzpatrick and Grant suggest that the mechanisms whereby vasoconstriction was induced *upstream* of the PA obstruction include either neural reflexes, or serotonin that reached the vasa vasorum of the main PA via the bronchial circulation (Fitzpatrick and Grant 1989).

Fitzpatrick and Grant described that left PA clamping produced a new reflection site very close to the main pulmonary artery with a reflection coefficient close to one (Weber, Janicki et al. 1983). Why did this increase in wave reflection combined with active pulmonary vasoconstriction, not produce greater increases in characteristic impedance? The explanation given is that the decrease in compliance due to vasoconstriction observed with PA clamping attenuates the increase in wave reflection associated with this manoeuvre (Grant and Lieber 1996; Fitzpatrick and Grant 1989). The nett result is that left PA occlusion induces minimal effects on wave reflection (Grant and Lieber 1996; Fitzpatrick and Grant 1989).

The above effects are in contrast to the increased wave reflection due to clots present in the pulmonary arterial tree that are present with thromboembolism. Pulmonary thromboembolism decreased characteristic impedance and pulse pressures. The reflected waves are not attenuated as with PA clamping, but magnified by the decrease in characteristic impedance of the pulmonary circulation (Grant and Lieber 1996; Fitzpatrick and Grant 1989). The reflected and forward waves summate and pulmonary artery pressure increases; the opposite happens with the flow waves and the forward flow rate decreases (Fitzpatrick and Grant 1989). The non-attenuated increase in wave reflection reduces hydraulic power output by the RV and induces systemic hypotension (Grant and Lieber 1996).

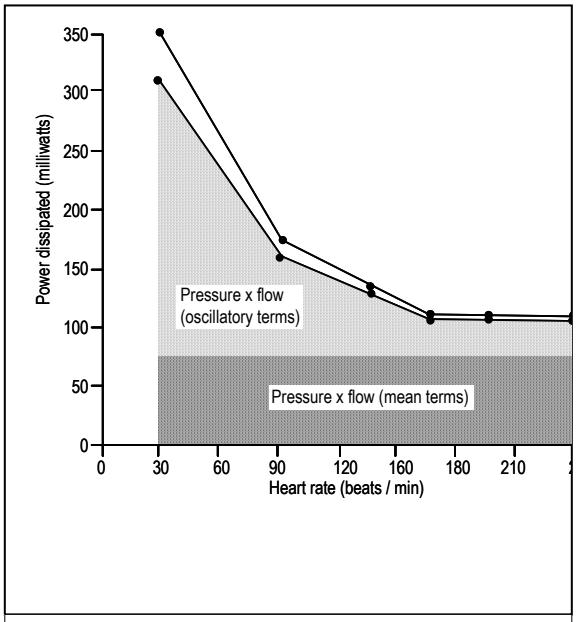


Figure 1.4.3.2.3. RV power output in the dog related to heart rate. The power is reduced as the heart rate reaches the frequency of the impedance minimum at 3 Hz (180 beats per minute). Redrawn from Piene, 1986

Pouleur and colleagues (Pouleur, Lefevre et al. 1978) also studied the difference between lung inflation and clamping of the left pulmonary artery on pulmonary input impedance. Clamping of the pulmonary artery and sustained lung inflation produced similar increases in the modulus of impedance at zero hertz. However, lung inflation slightly decreased (– 10%) while pulmonary artery clamping significantly increased (+ 77%) the impedance moduli over the 1 to 3 hertz range (Pouleur, Lefevre et al. 1978). As the pulmonary beds are in parallel with each other, clamping of one pulmonary artery should double the impedance moduli without producing phase changes (Figure 1.4.3.2.5). Pouleur and his colleagues observed that the impedance moduli increased by on clamping the PA; however this increase was to slightly less than double the pre-clamp values. They suggested that their findings concur with the aforementioned theoretical considerations if the pulmonary vascular adaptations of dilation and recruitment are taken into account (Pouleur, Lefevre et al. 1978).

The effect of an increase in transmural pressure on vascular impedance is difficult to predict. Arteries become stiffer as they distend. Vascular impedance is directly proportional to the stiffness (indirectly proportional to compliance) of the vessel wall (Nichols, Conti et al. 1977). This is supported by Fourie and co-workers who showed that characteristic impedance is '*strongly influenced by the compliance'* of the pulmonary artery (Fourie 1989). They induced pulmonary microvascular injury and pulmonary hypertension (PHPT) using glass beads (Fourie and Coetzee 1993; Fourie, Coetzee et al. 1992b; Fourie 1989; Calvin, Jr., Baer et al. 1985). Input impedance at zero frequency (PVR) increased (Fourie 1989; Calvin, Jr., Baer et al. 1985) but characteristic impedance was not changed by glass bead embolism (Calvin, Jr., Baer et al. 1985). This is in keeping with the differing effects of various manoeuvres on aspects of the pulmonary input impedance spectrum.

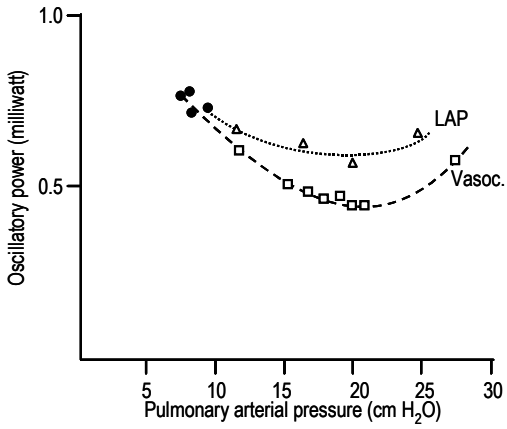


Figure 1.4.3.2.4. Oscillatory power in rabbit lungs versus pulmonary arterial pressure as the vasculature is progressively constricted from a state of maximal vasodilatation. Pulmonary input impedance attains a minimum at normal mean pulmonary arterial pressures of 15 to 20 mm Hg. "LA"P represents an increase in mean PAP due to increases in left atrial pressure and "vasoc." represents increases in mean PAP secondary to vasoconstriction of the PA. Redrawn from Piene, 1986.

The normal pressure in the pulmonary vascular bed assures an optimal balance between the oppositely directed influences on input impedance by vessel compliance and vessel diameter (Morpurgo 1995; Piene and Hauge 1976). Input impedance, as estimated by the oscillatory power generated to drive blood through rabbit lungs, has been shown to attain a minimum at normal mean pulmonary arterial pressures of 15 to 20 mmHg (Figure 1.4.3.2.4) (Piene 1986; Piene and Hauge 1976). It is most likely that this phenomenon is related to increases in pulmonary artery diameter caused by the existing pressure, albeit that this is accompanied by a decrease in PA compliance (see Womersley's equation (Equation 1.4.3.3)). However, above a mean PAP of 20 to 25 mmHg, the pulmonary artery approaches its elastic limit, PA compliance decreases exponentially (Fourie, Coetzee et al. 1992b; Fourie 1989; Reuben, Gersh et al. 1970) and consequently

the moduli of PA impedance increase (Milnor 1982c; Milnor, Conti et al. 1969) (Figure 1.5.4.3).

The relationships between the various elements comprising impedance have important physiological implications when considering the pulmonary vascular bed. The product of compliance and resistance is the time constant, tau (τ). Tau has been shown not to change over a wide range of resistance values in the pulmonary vasculature (Reuben, Swadling et al. 1971; Reuben, Gersh et al. 1970). Rueben et al. suggest that the uniformity of the time constant implies that compliance of the pulmonary arteries decreases to compensate for pre-capillary pulmonary vasoconstriction (Reuben, Swadling et al. 1971; Reuben, Gersh et al. 1970). However, in severe PHPT, the time constant of the PA will eventually lengthen when PVR increases beyond the limit that can be compensated for by a decrease in PA compliance (Reuben, Gersh et al. 1970).

The input impedance spectrum itself is independent of heart rate (Bergel and Milnor 1965; Reuben, Swadling et al. 1971). However, the fundamental harmonic for heart rate falls on the low frequency, steep part of the impedance versus frequency spectrum. The impedance for the first harmonic is twice as great when the heart rate is 60 (one

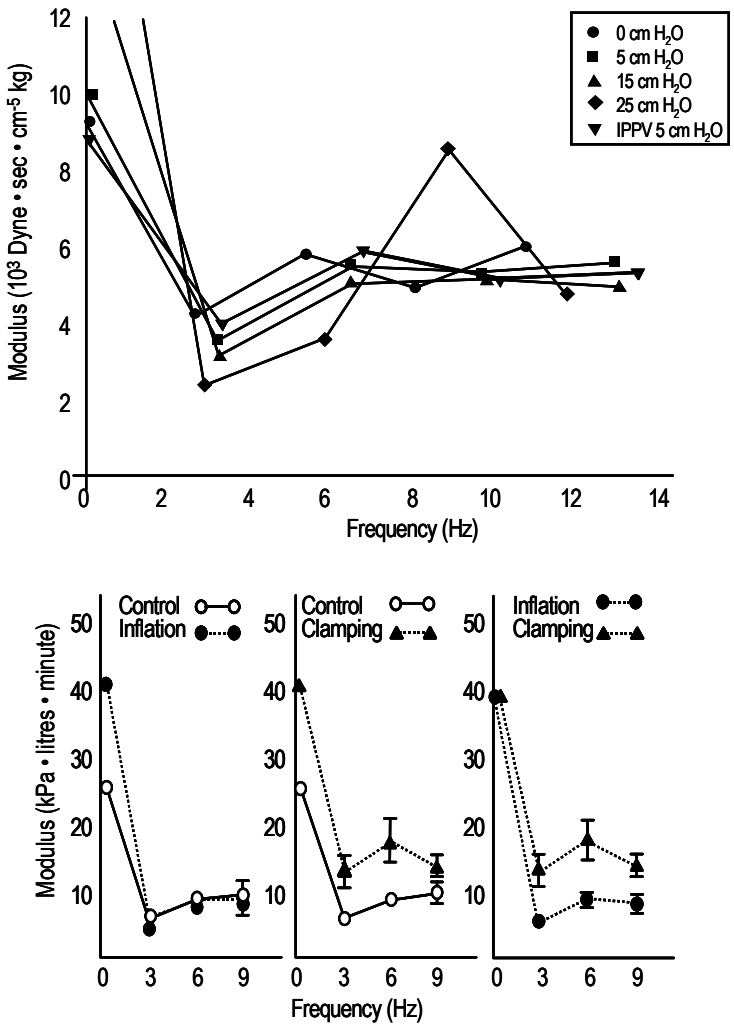


Figure 1.4.3.2.5.

Top: The pulmonary vascular impedance spectra in a dog at steady lung inflation of 0 to 25 cmH₂O and with IPPV to 5 cm H₂O. The impedance spectrum is the same during cyclic respiration and steady inflation to 5 cmH₂O. As pressure increases, impedance increases below 3 Hz and decreases between 3 to 6 Hz probably due to increased wave reflection from the compressed capillaries. Phase data are omitted as no significant changes occurred.

Bottom: Pulmonary input impedance spectra in dogs during steady lung inflation at 18 cmH₂O and during left PA clamping.

Top: Redrawn from Bergel and Milnor, 1965

Bottom: Redrawn from Pouleur, Lefevre et al, 1978

hertz) than when it is 120 beats per minute (Milnor, Conti et al. 1969). On the one end of the spectrum, the slower the heart rate is below one to two hertz, the greater the external cardiac work needed to eject a given stroke volume (Nichols, Conti et al. 1977; Milnor, Conti et al. 1969). On the other end of the spectrum, Milnor has shown that the power delivery of the RV falls as heart rate increases (Figure 1.4.3.2.3) (Piene 1986).

1.4.3.3 Is vascular impedance optimised in the normal lung?

Certain observations lead us to believe that impedance of the normal pulmonary vasculature *is* the optimal load for the right ventricle:

1. Physiological heart rates correlate with the impedance minima of various species (Piene 1986);
2. Impedance reaches a minimum at normal pulmonary artery pressures of 15 to 20 mmHg (Piene and Hauge 1976);
3. The theoretically calculated parameters of impedance (compliance, Zc and Rp) correlate closely with the measured parameters for maximal stroke volume and efficiency (Piene and Sund 1979);
4. The power output of the right ventricle is matched to the load presented by the pulmonary impedance or in other words,
5. The normal state is where the elastance of the pulmonary vasculature is less than half that of the right ventricle and the RV functions as a flow pump.

1.4.3.4 The use of pulmonary input impedance as an index of right ventricular afterload

Noordegraaf and Melbin suggest that if the product of pressure and area constitutes force, and if pressure is what the ventricle experiences during ejection, then the pressure in the vessels determines the force opposing shortening of the ventricular muscle fibres (Noordegraaf and Melbin 1978). However, as input impedance is a property of the arterial system that also takes the properties of the fluid being moved (i.e. viscosity and inertia) into account, it meets the requirements of a reliable index of arterial opposition to ventricular ejection external to the ventricle (Piene 1986; Parbrook, Davis et al. 1985; Milnor 1975). Therefore, Noordegraaf and Melbin incorporated input impedance as a component in their comprehensive definition of afterload. They suggest that the time varying increase in ventricular pressure $\Delta P_v(t)$ be considered to be equal to the (time varying) ejection flow Q(t) convoluted[#] with input impedance $Zin(\omega)$:

$$\Delta P_v(t) = Q(t) * Zin(\omega) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.4.3.4.1}$$

Where

$Zin(\omega)$ is input impedance at a particular frequency (in other words a frequency domain index of afterload whereas the other terms in this equation represent time domain indices) and,

$*$ represents the mathematical process of convolution.

[#] "Convolution" is a mathematical procedure allowing multiplication of time dependent and frequency dependent quantities (Noordegraaf and Melbin, 1978). It is represented by the symbol $*$ in section 1.4.3.4.

During the ejection phase, pulmonary arterial $P_a(t)$ and right ventricular pressures $P_v(t)$ can be expressed as

$$P_a(t) = P_v(t) = P_{Diastole} + Q(t) * Zin(\omega) \quad \text{..... Equation 1.4.3.4.2}$$

Where

$P_{Diastole}$ is diastolic pressure in the PA.

Equation 1.4.3.4.2 describes afterload as varying with time throughout systole. Until ejection occurs, afterload rises continuously with time and factors external to the ventricle do not play a role (flow is zero). However, factors external to the ventricle (well described by input impedance) then play a role during ejection into the arterial system. What is also incorporated in this concept of afterload is that during ventricular ejection, ventricular volume decreases. If force is the product of pressure and area, and if pressure were constant during ejection, the forces opposing shortening of the ventricular muscle fibres would therefore decrease. This definition of afterload is noteworthy in three ways. Firstly, it incorporates input impedance as one element of its definition. Secondly it emphasizes that afterload varies with time and ventricular volume throughout the period of systole. It could be speculated that equation 1.4.3.4.2 could be modified to incorporate a time dependent variable of afterload such as an index of resistance (Rp, Zc or R_{TOTAL}) or, arterial elastance (Ea) (see section 1.4.4), which can be considered the time domain (Fourie 1989) representation of input impedance. Thirdly, this definition is applicable to both the right and left sides of the circulation (Noordergraaf and Melbin 1978).

1.4.3.5 Pulmonary input impedance and right ventricular performance

An increase in the moduli of input impedance can be reliably considered as an increase in afterload as it raises the external work done by the ventricle and influences ventricular performance. Elzinga and Westerhof (Elzinga and Westerhof 1973) showed that when input impedance in the aorta increased, left ventricular pressure increased and ventricular stroke volume fell (Grant and Lieber 1996; Milnor 1982a; Elzinga and Westerhof 1973). Calvin et al. (Calvin, Jr., Baer et al. 1985) have demonstrated that a similar inverse relationship between RV stroke volume and PA input impedance exists. The cause of the increase in impedance did not make a difference to right ventricular performance.

1.4.3.6 Limitations of input impedance as an index of right ventricular afterload

Sagawa suggests that arterial impedance has not been widely used as a measure of ventricular afterload as its physiological meaning is hard to grasp without the proper background (Sagawa, Maughan et al. 1988). Furthermore, measurement of arterial and pulmonary vascular impedance, particularly in humans, is difficult (Parbrook, Davis et al. 1985).

1.4.4 Effective arterial elastance as an index of afterload (Ea)

Ea may be modelled mathematically in the following way. From the concept of a direct current circuit, (Fourie, Coetzee et al. 1992a; Sagawa, Maughan et al. 1988; Sunagawa, Maughan et al. 1985; Sunagawa, Maughan et al. 1983), where potential difference is equal to the product of mean flow multiplied by total resistance, we can see that

$$Pmean = R_{TOTAL} \times Q \quad \text{..... Equation 1.4.4.1}$$

Where

Pmean is the mean pressure

R_{TOTAL} is the total resistance of the vascular circuit, the sum of Rp and Zc in the 3 element Windkessel model of the circulation, and

Q is the mean (time averaged) flow in the circuit.

Pmean approximates end systolic pressure (Pes). Furthermore Q ($ml.min^{-1}$) is equal to SV divided by the time per cardiac cycle length (T). (T = seconds per beat / 60), i.e.:

$$Q = SV / T \quad \text{..... Equation 1.4.4.2}$$

Then from Equations 1.4.4.1 and 1.4.4.2

$$Pes \approx R_{TOTAL} \times SV / T \quad \text{..... Equation 1.4.4.3}$$

Thus the slope of the Pes-stroke volume relationship, which is effective arterial elastance (Ea), is approximated by

$$Ea \approx R_{TOTAL} / T \quad \text{..... Equation 1.4.4.4}$$

Another way of expressing Ea is in combination with the three parameters of the modified Windkessel model. If the area under one arterial pressure cycle (A_T) divided by the time of one cardiac cycle (T) is used to calculate Pmean, then from Equations 1.4.4.1 and 1.4.4.3

$$R_{TOTAL} = \frac{Pmean}{Q} = \frac{A_T / T}{SV / T} \quad \text{..... Equation 1.4.4.5}$$

If we simplify the preceding equation, we get

$$SV = A_T / R_{TOTAL} \quad \text{..... Equation 1.4.4.6}$$

By inspecting Figure 1.4.4.1, we can assume that the area under the systolic curve approximates a rectangle, thus

$$As \approx Pes \times ts \quad \text{..... Equation 1.4.4.7}$$

The diastolic area Ad can be described by (Sagawa, Maughan et al. 1988)

$$Ad = Pes \times \tau (1 - e^{-td/\tau}) \quad \text{..... Equation 1.4.4.8}$$

Where

τ is the time constant of diastolic arterial pressure decay that equals compliance of the system multiplied by resistance. The derivation of Equation 1.4.4.8 is given in the appendix of this document.

We may add the last two equations together to describe the total area subtended by the arterial pressure curve (A_T). This reveals that

$$A_T = Pes [ts + \tau(1 - e^{-td/\tau})] \quad \text{..... Equation 1.4.4.9}$$

If we substitute equation 1.4.4.9 into equation 1.4.4.6, then

$$SV \times R_{TOTAL} = Pes [ts + \tau(1 - e^{-td/\tau})] \quad \text{..... Equation 1.4.4.10}$$

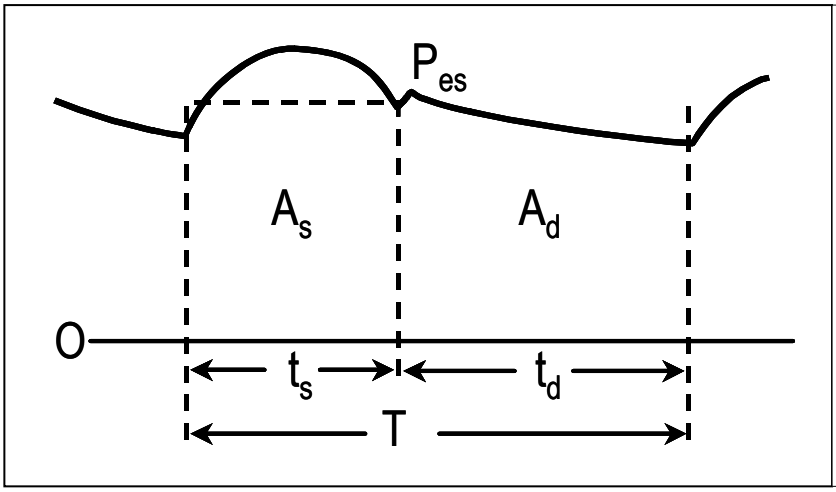


Figure 1.4.4.1. A schematic diagram of an arterial pressure curve. The area subtended by systole is designated As, and diastole Ad. ts and td designate systolic and diastolic times respectively. T is the time of one cardiac cycle. Redrawn from Sagawa, Maughan et al, 1988.

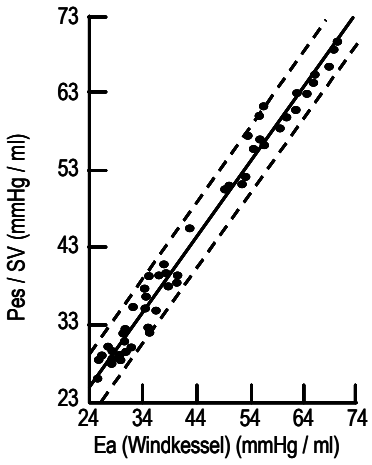


Figure 1.4.4.2. The correlation between pulmonary Ea as measured by Pes/SV and as calculated by Equation 1.4.4.12 containing the elements of the modified windkessel model. r = 0.997; n = 62; p <0.001. Redrawn from Fourie and Coetzee, 1992

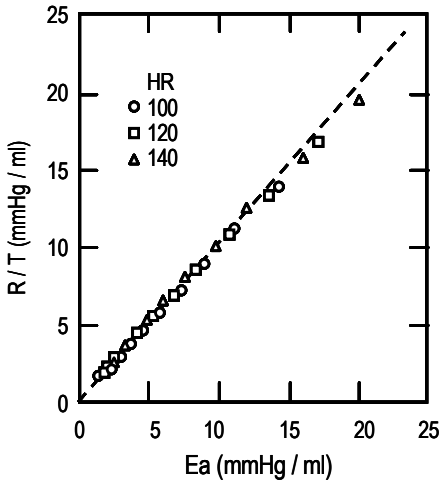


Figure 1.4.4.3. The correlation between Ea as measured by Rtotal/T and that measured by the relationship of R_0/ T. r = 0.99; n = 33; p <0.0001

Redrawn from Sunagawa, Maughan et al, 1988

Solving for Pes:

$$Pes = \frac{SV \times R_{TOTAL}}{ts + \tau(1 - e^{-td/\tau})} \quad \ldots\ldots\ldots\ldots \quad \text{Equation 1.4.4.11}$$

If Ea is Pes /SV, then

$$Ea = R_{TOTAL} / (ts + \tau(1 - e^{-td/\tau})) \quad \ldots\ldots\ldots\ldots \quad \text{Equation 1.4.4.12}$$

Where in terms of the Windkessel model, the three elements are

Tau (τ) which is R_{TOTAL} x C and,

R_{TOTAL}, which is the sum of Rp and Zc (Fourie 1989).

Another approach is to conceptualise the arterial tree as if it were an elastic chamber that accommodates a certain volume of blood during each beat (Sunagawa, Maughan et al. 1985). Arterial elastance therefore represents the pressure change of the arterial tree in accommodating the stroke volume and can be derived from the slope of the relationship of end systolic pressure (Pes) to stroke volume (Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992; Sagawa, Maughan et al. 1988).

$$Ea = Pes / SV \quad \ldots\ldots\ldots\ldots \quad \text{Equation 1.4.4.13}$$

Ea calculated by the above equation or measured by using Pes/SV or R_{TOTAL}/T is highly linear. Furthermore, a strong correlation exists between the various methods of determining Ea (Figures 1.4.4.2 and 1.4.4.3). Therefore, although the slope is accurately described by the Pes/SV relationship, Ea contains more complex elements than simply the relationship of pressure to volume. It also does not simply represent the inverse of compliance of an arterial system (Sagawa, Maughan et al. 1988). From Equation 1.4.4.12 it can be seen that Ea includes components of resistance, compliance and time (heart rate), and is justifiably termed the ***'effective'*** arterial elastance (Sagawa, Maughan et al. 1988). A further illustration of the complex nature of Ea is illustrated in Figure 1.5.4.2: Ea is more affected by changes in peripheral resistance than by changes in compliance of the relevant arterial tree (Sunagawa, Maughan et al. 1983).

Ea may also be considered as the time domain representation of the pulmonary artery input impedance. Fourie (Fourie 1989) has confirmed that Ea incorporates the lumped parameters (Ro, Rp, and C) of the Windkessel model for the right side of the circulation (compare Equations 1.4.3.1.1 and 1.4.4.12).

1.5 Coupling of the ventricle to its load

In 1975 Milnor wrote: "*Adopting arterial impedance as the operational definition of afterload may solve one problem, but it leaves another crucial question unanswered. How can we put afterload and inotropic state into commensurate terms? What is required is an expression of afterload that can be correlated with some description of contractile state; such an expression has not yet been developed (Milnor 1975)*." This problem may be addressed by utilizing the concept of ventricular-arterial coupling.

The concept of ventricular-arterial coupling is analogous to that of two elastic "balloon" like structures, the one (the ventricle) periodically becomes stiffer than the other (the arterial system) and transfers a volume of blood into it (Maughan and Oikawa 1989). If the elastances of each of the two chambers are known, then prediction of how much volume is transferred between the two is possible

The one balloon is the ventricle. Ventricular stiffness is described by the end systolic elastance of the ventricle, Ees. Ees describes the slope of the ventricular Pes-SV relationship. It is a linear and load independent descriptor of ventricular contractile function. The other balloon is the arterial circulation. Its stiffness is described by the effective arterial elastance, Ea (Sunagawa, Maughan et al. 1985).

The stroke volume that results from the interaction (coupling) of *various* Ea and Ees values can be mathematically described from the pressure versus volume diagrams (Sunagawa, Maughan et al. 1983). To mathematically describe the interaction between Ees and Ea, we need to define the lines Ees and Ea. Ea has been defined already. From Figure 1.5.1 (Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992a; Sagawa, Maughan et al. 1988; Piene and Myhre 1984; Sunagawa, Maughan et al. 1983; Sagawa 1978),

$$Ees = Pes / (Ved - SV - Vo) \quad \text{..... Equation 1.5.1}$$

Where

Ved is end-diastolic volume of the ventricle, and

Vo is the volume intercept of Ees.

From Equation 1.4.4.3 ($Pes \approx R \times SV / R_{TOTAL}$) and Equation 1.5.1

$$Ved - SV - Vo = Pes/Ees = R \times SV / T \quad \text{..... Equation 1.5.2}$$

If $Ea \approx R / T$, then

$$Ved - SV - Vo = Pes/Ees = Ea/Ees \times SV \quad \text{..... Equation 1.5.3}$$

Rearranging and solving for SV

$$Ea/Ees \times SV + SV = Ved - Vo$$

Simplifying

$$SV (1 + Ea/Ees) = Ved - Vo$$

$$\therefore \quad SV = \frac{(Ved - Vo)}{1 + Ea/Ees} \quad \text{..... Equation 1.5.4}$$

Equation 1.5.4 has been verified to be valid and accurate in experimental models (Figures 1.4.4.2 and 1.4.4.2.3) (Coetzee and Fourie 1993; Maughan 1988; Sagawa, Maughan et al. 1988; Sunagawa, Maughan et al. 1983). Because the units of Ees ($mmHg.ml^{-1}$) are the same as those of arterial elastance, the elastic properties of these structures and the interaction between the two can be depicted on one common set of axes (Figure 1.5.1). Adding a representation of the pressure-volume relationship of the ventricle to the aforementioned graph gives a more complete picture of the interaction between Ea and Ees (Weber, Janicki et al. 1983). This graphical representation can be useful as an intuitive tool to describe the effect of changes in various parameters (e.g. Ea, Ees, end-diastolic volume of the ventricle) on stroke volume (Figures 1.5.2 and 1.5.2.10) (Sagawa, Maughan et al. 1988; Burkhoff and Sagawa 1986; Sunagawa, Maughan et al. 1985; Sunagawa, Maughan et al. 1983). These representations have been developed for the LV, however the concept has been demonstrated to also apply to the right ventricle (Fourie, Coetzee et al. 1992b; Fourie 1989).

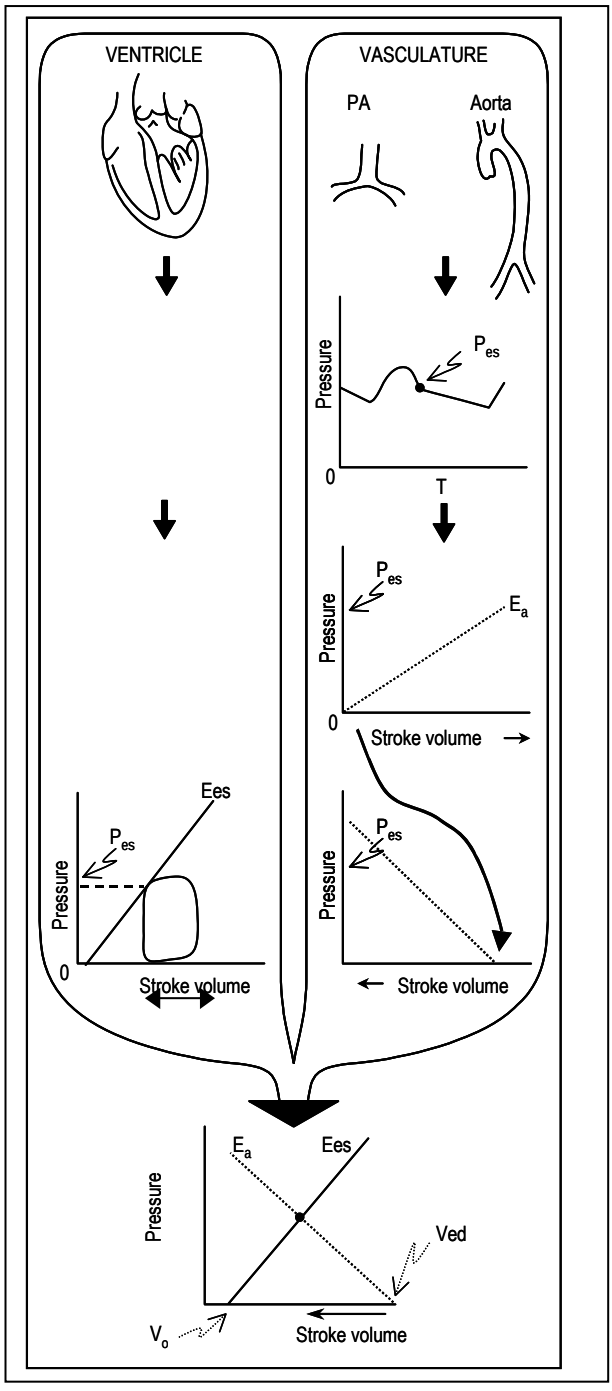


Figure 1.5.1. A diagrammatic representation of coupling of the ventricle to its load. Mechanical characteristics of the ventricle are expressed in the left hand column as the relationship between pressure and volume generated by the ventricle, and those of the vasculature as the relationship of pressure in the arterial tree versus time. However, the characteristics of the arterial tree can also be expressed as the relationship between the volume inputted into it and the resultant arterial pressure. The ratio between pressure and volume in a chamber is termed its elastance. If the elastances of these two chambers are expressed in terms of pressure and volume, then the properties of these two chambers can be expressed on the same axes. The relationship between ventricular pressure and volume (i.e. ventricular elastance) is represented by the end-systolic elastance (Ees) line. The relationship between vascular pressure and volume (i.e. arterial elastance) is represented by the arterial elastance (Ea) line. These relationships apply to the left ventricle and its vascular tree as well as the right ventricle and its vascular tree. Ved is end-diastolic volume of the ventricle and Vo is the intercept of the Ees line with the axis representing ventricular volume. Redrawn and adapted from Sunagawa, Maughan et al, 1985.

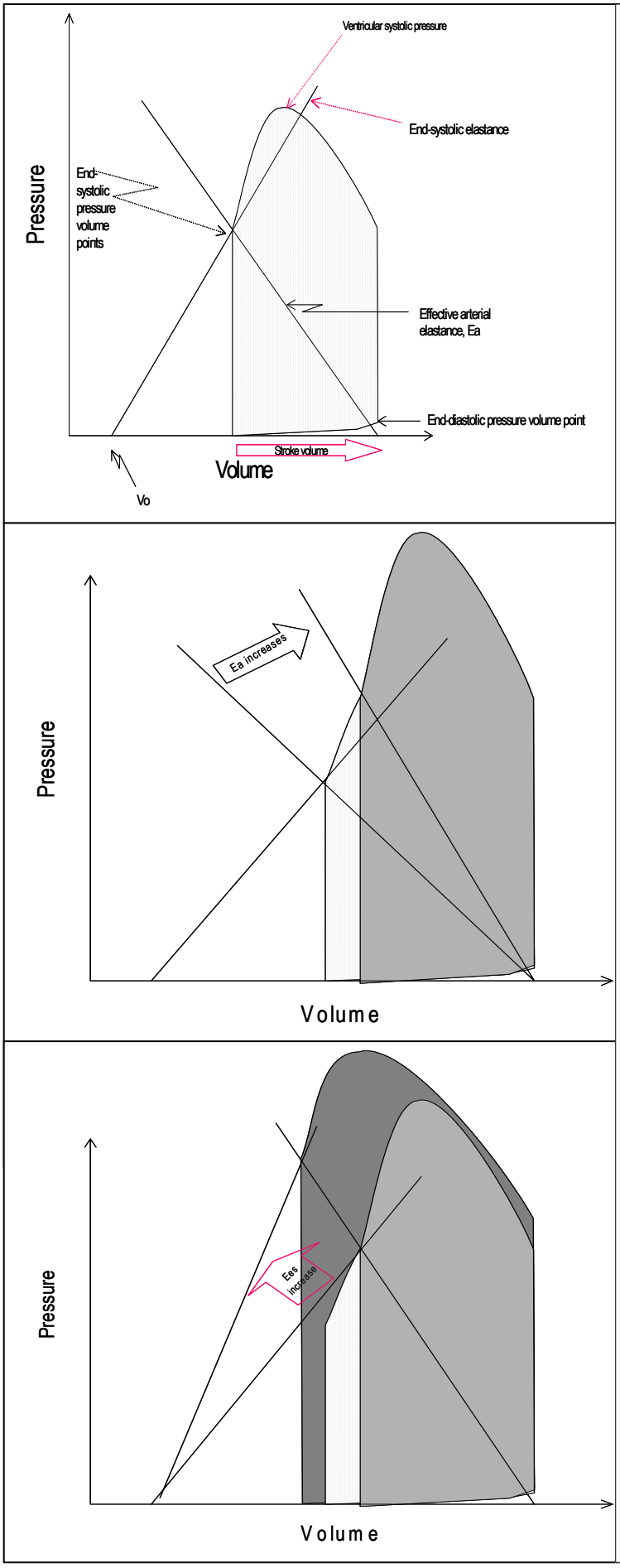


Figure 1.5.2

These figures represent three ventricular pressure-volume relationships.

Top: The top diagram represents the normal situation. Ea and Ees are normal. The various annotations in the top diagram are omitted in the bottom two for the sake of clarity.

Middle: afterload (Ea) is increased at an Ees that is unchanged from baseline. An increase in Ea is represented by an increase in the slope of the line representing Ea. It can be observed that, if the end-diastolic volume is kept the same, stroke volume decreases as Ea increases. Systolic pressure generated by the ventricle increases.

Bottom: The diagram at the bottom on the left represents the effects of increasing Ees in the face of an increase in Ea. An increase in Ees is represented by an increase in the slope of the line representing Ees. If end-diastolic volume is kept constant, the effect of increasing end-systolic elastance in the face of an increase in Ea is to increase both systolic pressure and stroke volume. Furthermore, if stroke work is the product of mean arterial pressure and stroke index (i.e. the area under the pressure volume lop), it can be graphically seen that the area subtended by the pressure-volume loop increases in this scenario. Therefore, an increase in Ees of a ventricle facing an increase in arterial elastance results in it being able to generate an increase in stroke work.

1.5.1 The relationship of coupling of the ventricle to its load, and heart rate

Sagawa and colleagues (Sagawa, Maughan et al. 1988) mathematically relate coupling of the ventricle to its load, and heart rate in the following manner. From Equation 1.5.4:

$$SV = \frac{Ees\,(Ved - Vo)}{Ees + Ea} \qquad \text{Equation 1.5.1.1}$$

Where

Ees = end-systolic elastance,

Ved = end-diastolic volume,

Vo = volume of the ventricle when the intracavitary pressure is zero and,

Ea = effective arterial elastance.

Cardiac output is the product of stroke volume and heart rate. Cardiac output may also be derived by dividing stroke volume by cardiac cycle length "T". Therefore dividing equation 1.5.1.1 by "T" to obtain cardiac output gives the following relationship:

$$CO = \frac{Ees\,(Ved - Vo)}{T(Ees) + R_{TOTAL}} \qquad \text{Equation 1.5.1.2}$$

The pressure is generated by the numerator, "*Ees x (Ved – Vo)*". The arterial load becomes a simple resistance, R_{TOTAL}. The internal resistance of the ventricle is the product of *T* and *Ees.*[#] Thus, any increase in contractility will on the one hand, increase the pressure generated but on the other hand, also increase the internal resistance in the generator. Such an increase in the internal resistance limits the increase in cardiac output. However, an increase in heart rate shortens T and decreases the internal resistance of the generator. The effect of this increase in heart rate will be to increase cardiac output if the end-diastolic volume remains constant (Sagawa, Maughan et al. 1988).

Piene has also suggested that the frequency at which the impedance minimum occurs correlates well with the physiological heart rates of various species (Piene 1986). Therefore at physiological heart rates, opposition to ventricular ejection is significantly influenced by both heart rate (impedance) and the status of the peripheral vasculature (resistance) (Milnor, Conti et al. 1969). It is interesting that the concepts both coupling of the ventricle to its load and impedance to pulmonary flow (see last two paragraphs of section 1.4.3.2) can be linked to heart rate.

[#] The products of "*T and Ees*" and "*T and Ea*" can be equated with resistance to flow if the following is considered. "*T"* is time per beat and the *elastances "Ees and Ea"* are relationships of pressure to volume. *For example, for the product of Ees and T*

T x Ees = Time x (Pressure/Volume) ..... Equation y

Equation y simplifies to

T x Ees = Pressure/Flow ..... Equation z

Pressure/Flow is analogous to resistance. The same can be shown for Ea.

1.5.2 Use of coupling to study right ventricular efficiency and stroke work

The ventricle can be considered as a pump that generates hydraulic[#] power (Asanoi, Sasayama et al. 1989; Piene and Sund 1982). Power is transferred to the blood in the ventricle which is moved into the receiving system, the arterial load (Asanoi, Sasayama et al. 1989; Piene and Sund 1982).

The term 'matching' is borrowed from electrical theory. According to electrical theory, a generator and its load are optimally matched when the power delivered from the generator to the load is maximal (Asanoi, Sasayama et al. 1989; Piene 1986; Myhre, Johansen et al. 1986). The graph of work versus load typically describes a concave curve (Figure 1.5.2.1) (Myhre, Johansen et al. 1986). Optimal matching of a pump occurs when the work done and load it has to operate against, correspond to a point at the summit of the curve. This point corresponds to the relationship between a pump and its load where the energy transfer is maximal (Piene and Sund 1982).

Sunagawa et al. (Sunagawa, Maughan et al. 1985) studied arterial resistance versus stroke work in the isolated left ventricle. SW peaked at a certain arterial resistance: if resistance increased or decreased from this point, stroke work decreased (Figure 1.5.2.1). As preload was increased, the maximal stroke work that could be delivered increased, but the arterial resistance at which it occurred did not increase concomitantly. However at a particular preload, as contractility was increased, the optimal arterial resistance at which maximal stroke work occurred also increased. This may be understood if one considers ventricular-arterial coupling (Figure 1.5.2). An increase in Ees will enable the ventricle to cope with an increase in the slope of Ea (afterload). However, an increase in end-diastolic volume will increase stroke volume and work but not change the slope of Ees, or the Ea that that ventricle can accommodate (Sunagawa, Maughan et al. 1985).

The relationship between right ventricular ability to generate work and its afterload (i.e. the coupling of right ventricle and the pulmonary circulation) is similar to that of the left ventricle (Fourie, Coetzee et al. 1992b; Fourie 1989). The difference between left and right ventricles lies in the more limited ability of the RV to generate work. Right ventricular end-systolic elastance normally ranges between 1 to 2 mmHg.ml^{-1} and right ventricular stroke work peaks at an Ea of approximately 2 mmHg.ml^{-1} (Fourie, Coetzee et al. 1992b). SW in the thicker left ventricle peaks at an Ees of approximately 7 mmHg.ml^{-1} (Sagawa, Maughan et al. 1988; Burkhoff and Sagawa 1986) (Figures 1.5.2.2 and 1.5.2.3).

Another criterion for the evaluation of coupling between a power source and its load is how efficiently the transfer of energy occurs i.e.:

- The ratio of the energy supplied to the system and the usable energy delivered by the system (Sagawa, Maughan et al. 1988) i.e. the ratio of $\frac{\text{energy expended}}{\text{work delivered}}$ or,
- How efficient the fuel consumption is (Asanoi, Sasayama et al. 1989).

[#] Hydraulics: the branch of physics that deals with the actions of liquids in pipes (Chambers Dictionary, 1992; Dorland's Medical Dictionary 25th Edition)

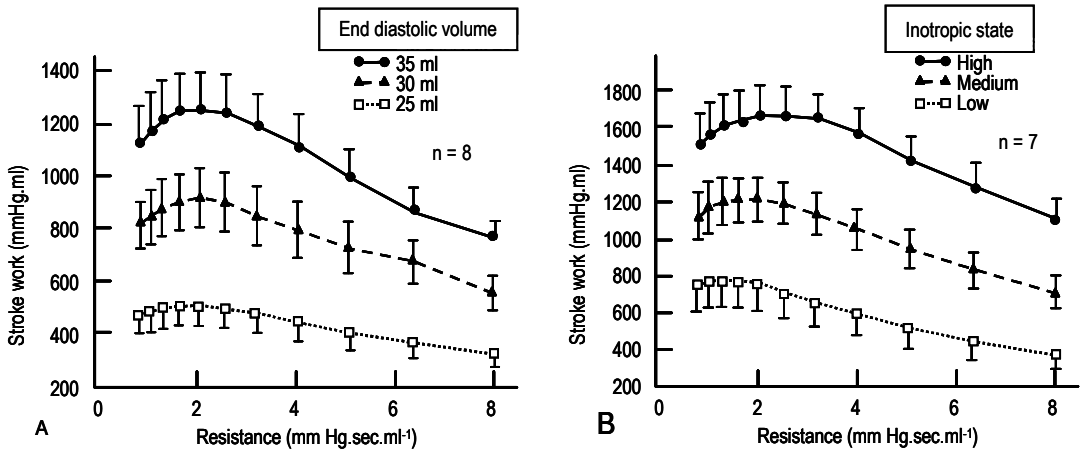


Figure 1.5.2.1. Plot of SW versus arterial resistance for various end-diastolic volumes and contractile states of the isolated canine left ventricle. Redrawn from Sunagawa, Maughan et al, 1985.

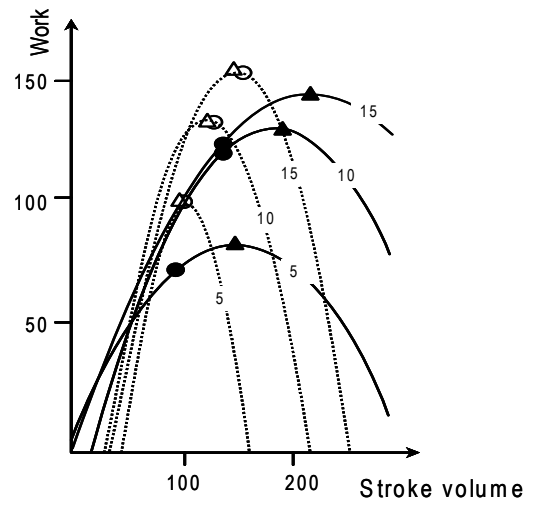


Figure 1.5.2.2. Parabolas of work (mmHg.ml) versus stroke volume (ml) at three levels of right atrial pressure (5, 10, 15 mmHg) before (dotted parabolas) and after depression of the ventricle. Using the following two equations,

- *Pes = Ees (EDV-SV-Vd), and*
- *W = Pes x SV*

Myhere, Johansen, et al. showed that if Ees and preload are constant, then the following equation describes a concave parabola relating work to stroke volume.

$W = Ees\ (EDV-Vd) \times SV - (Ees \times SV^2)$

Triangles: maximum point; Circles: control point. Axes are graded in terms of percentages of control observations at RAP 5 mmHg.

Redrawn from Myhere, Johansen, et al. 1988

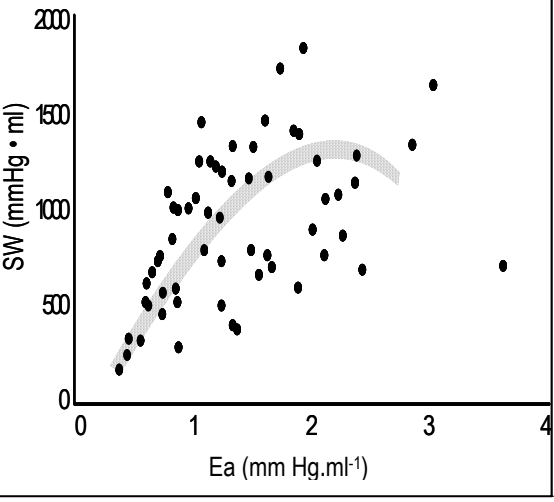


Figure 1.5.2.3. The relationship between Ea and SW for the right ventricle is represented in this diagram on the left. Opposition to right ventricular ejection was increased b\y injecting glass beads into the pulmonary vascular bed. In this diagram, afterload is represented by pulmonary arterial elastance.

Redrawn from Fourie, Coetzee et al, 1992

A system is considered efficient when minimal loss of energy occurs when transferred (Figure 1.5.2.4). Only a small fraction of the total amount of energy generated by any specific pump system is usually actually transferred to the load (Piene and Sund 1982). Maximal efficiency of the normal heart is reported to be only 25% to 30% and normally operates between 5 to 20% efficiency (Sagawa, Maughan et al. 1988).

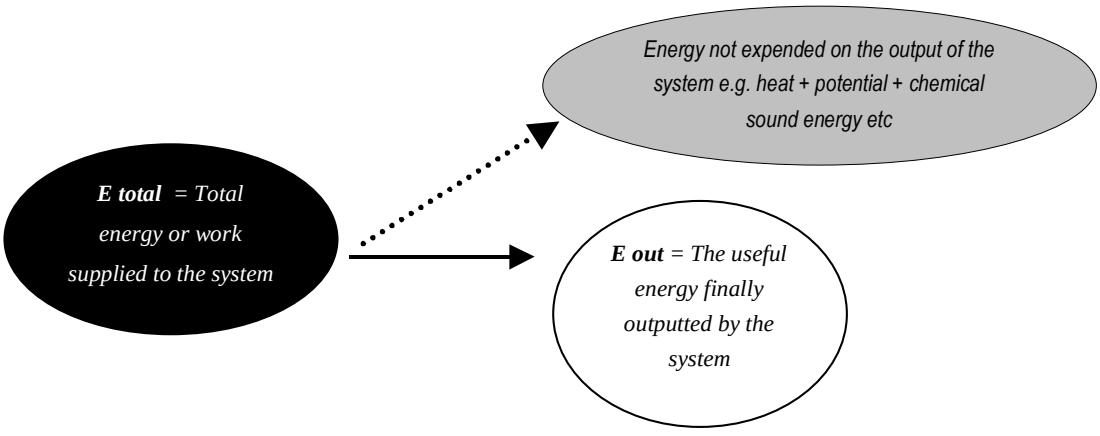


Figure 1.5.2.4. A diagram illustrating the concept of efficiency.

Efficiency = E out /E total (Note that for the heart, E out is the external mechanical work performed.)
E total = E out + (E heat +potential +chemical +sound etc.)

The mechanical work done on the blood in the ventricle can be considered the useful energy outputted by this system (Sagawa, Maughan et al. 1988). Efficiency can therefore be defined as the ratio of external stroke work performed, to the total work done (or used by) a ventricle (van den Horn, Westerhof et al. 1985).

The total amount of mechanical work done to move the stroke volume into its arterial load is the sum of (Figures 1.5.2.4 and 1.5.2.5):

1. The external stroke work (SW) represented by the area "SW" in figure 1.5.2.5 and,
2. Creation of the potential energy (PE) that remains in the ventricle at the end of ejection. (Potential energy is represented by area PE in figure 1.5.2.5). The sum of the areas SW and PE are termed the pressure-volume area (PVA). Efficiency can therefore be considered the ratio of SW / PVA.

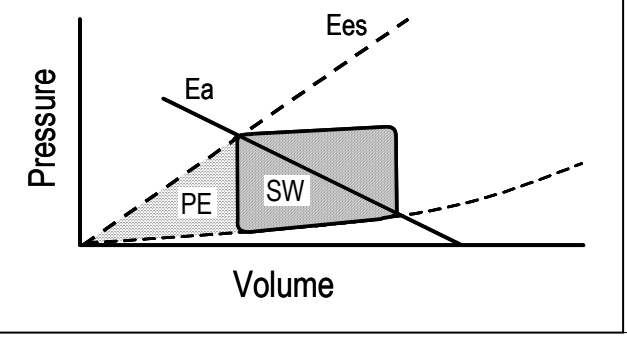


Figure 1.5.2.5. Pressure volume relationship superimposed upon a diagram of ventricular-arterial coupling. Total mechanical work is represented by the area PVA.

PVA = SW + PE.

Modified from Asanoi, Sasayama et al, 1989

Furthermore, the energy used by the heart is represented by myocardial oxygen demand (MVO_2[#]) (Sagawa, Maughan et al. 1988). Suga has shown that MVO_2 is linearly related to PVA with a co-efficient of determination (r^2) of 0.72 (Fourie, Coetzee et al. 1992b; Asanoi, Sasayama et al. 1989; Burkhoff and Sagawa 1986; Suga, Hayashi et al. 1981). The remaining 28% depends on factors not included by PVA and Emax (Burkhoff and Sagawa 1986). However, mechanical efficiency of a ventricle may, with reasonable accuracy, also be considered as the ratio of the external stroke work to MVO_2 (Asanoi, Sasayama et al. 1989; Sagawa, Maughan et al. 1988). Fourie, Coetzee et al. have applied this to the right ventricle also (Fourie, Coetzee et al. 1992b).

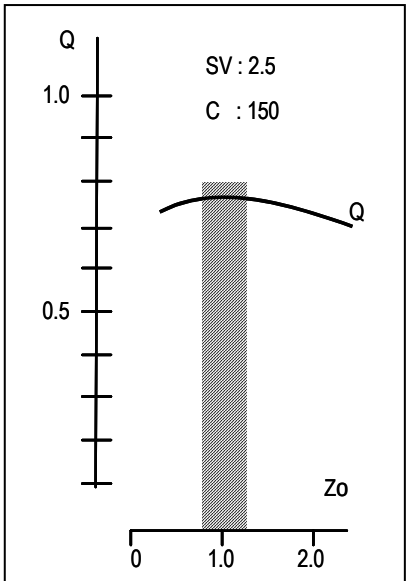


Figure 1.5.2.6. The relationship between pump efficiency (Q) and characteristic impedance (Zo) in the isolated cat right ventricle. Adapted from Piene and Sund, 1982

As afterload increases, the efficiency of the ventricle reaches a peak: further increases in afterload result in a decline in efficiency. This is applicable to both right (Figure 1.5.2.6) (Fourie, Coetzee et al. 1992b) and left (Figure 1.5.2.7) (Sunagawa, Maughan et al. 1985) ventricles facing increasing afterload. However, as Ees increases, the load with which the ventricle can cope also increases and therefore the load that corresponds to maximum efficiency also increases. Efficiency of the ventricle working against a particular load also increases with increases in Ees (Figure 1.5.2.9).

A number of studies have been performed to answer questions pertaining to the coupling of the ventricle to its load. One important question is whether arterio-ventricular coupling, under normal circumstances *in vivo,* results in the system functioning at maximal efficiency or maximal stroke work (Asanoi, Sasayama et al. 1989; van den Horn, Westerhof et al. 1985).

Sunagawa made one of the first attempts to answer this question. He hypothesized that maximal energy transfer would occur from one elastic chamber to another (i.e., right or left ventricle to its respective arterial system) when their elastances are equal. This hypothesis was subsequently verified to apply to both isolated left (Myhre, Johansen et al. 1986; Sunagawa, Maughan et al. 1985; van den Horn, Westerhof et al. 1985) and right (Piene and Sund 1982) ventricles for a variety of loading conditions, contractile states and heart rates. The suggestion was then made that the isolated right (Fourie 1989; Piene 1986; Piene and Sund 1982; Piene and Sund 1979) and left ventricles (Myhre, Johansen et al. 1988; Myhre, Johansen et al. 1986; Sunagawa, Maughan et al. 1985; Sunagawa, Maughan et al. 1983) normally operate at the peak of the maximal stroke work versus load curve. If this were true, it would predict that firstly ventricular and arterial elastances would normally be equal (Coetzee and Fourie 1993;

[#] Note that "VO_2" is used throughout the thesis to indicate "oxygen consumption per unit time" instead of the more conventional "□O_2".

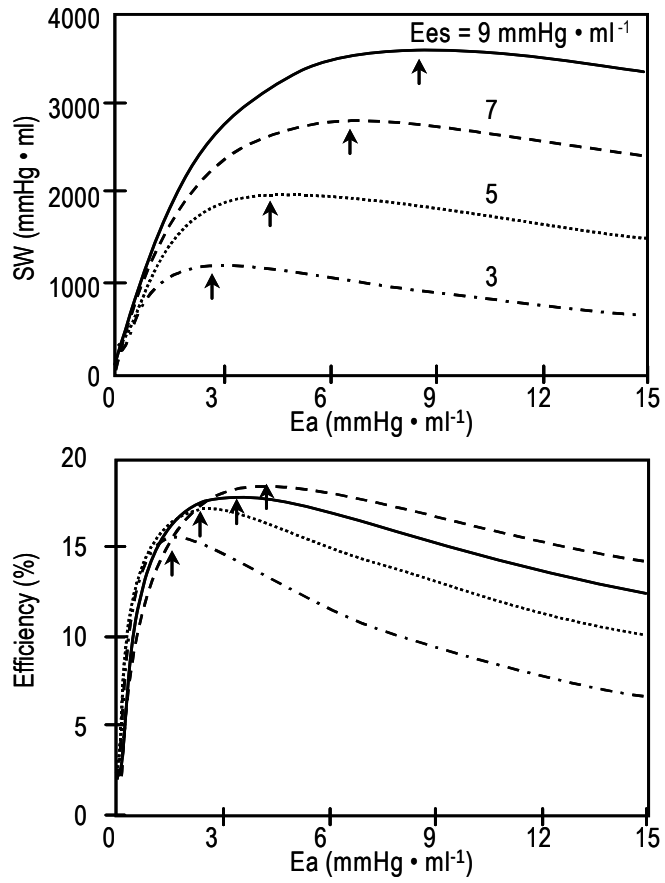


Figure 1.5.2.7. The relationship between Ea and stroke work for a left ventricle with various levels of contractility as indicated by the various Ees levels. Actual left ventricular Ees as measured in isolated canine ventricles (Sunagawa, Maughan et al. 1985) varied from 4,1 +/- 1.1 to 7,5 +/- 2.3 mmHg.ml^{-1}. The arrows in the top diagram indicate the point of maximal stroke work and efficiency in the top and bottom diagrams respectively. When coupling moves beyond (to the right of) the maximal point of the relationship between SW and Ea for a particular Ees level, the ventricle is considered to be failing. Note that increasing contractility shifts this relationship higher and to the right. In other words, the ventricle can better cope with its load. Improving contractility improves the ventricles efficiency for a particular load.

Redrawn from Burkhoff and Sagawa, 1986

Fourie, Coetzee et al. 1992a; Asanoi, Sasayama et al. 1989; Maughan 1988; Sagawa, Maughan et al. 1988; Sunagawa, Maughan et al. 1985; van den Horn, Westerhof et al. 1985; Piene and Sund 1982; Sunagawa, Maughan et al. 1985) and secondly that the ejection fraction of a normal ventricle would be 50% (Sunagawa, Maughan et al. 1985; Sunagawa, Maughan et al. 1983). However, this is an underestimate of ejection fraction in the normal LV.

This question was also addressed by Burkhoff and Sagawa (Burkhoff and Sagawa 1986). Similar to the approach used by Sunagawa, Maughan and colleagues, they utilized a hypothetical model of the left ventricle[#] to examine whether work or efficiency was maximal during normal physiology (Figure 1.5.2.7). They found that when Ea = Ees, the end-diastolic volume and the end-systolic pressure of the hypothetical ventricle would be much larger, and the ejection fraction less, than what actually occurred during normal physiology. They concluded that in order to obtain physiological conditions, Ea must be smaller than Ees, and that this state represents normal physiology. Their hypothesis was subsequently verified for the *isolated* left (Sunagawa, Maughan et al. 1985; van den Horn, Westerhof et al. 1985) and right ventricles (Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992b; Fourie 1989; Piene and Sund 1982). Asanoi et al. (Asanoi, Sasayama et al. 1989) subsequently confirmed the concept that Ea is less than Ees in the normal human left ventricle (in vivo) possessing an ejection fraction of more than 60%. Asanoi showed

[#] Burkhoff and Sagawa (Burkhoff and Sagawa 1986) used the formulae derived above for Pes and Ea, using the lumped element Windkessel model, and the aforementioned concepts for stroke work and efficiency. The constants assumed were Ees = 7 mHg.ml^{-1}, Ved = 45 ml, Vo = 5 ml and Ea was varied from 0 to 15 mmHg.ml^{-1}.

that in intact humans with *ventricles having mildly depressed contractility*, ventricular-arterial coupling was set to deliver maximal stroke work rather than maximal efficiency (compare scenario in the preceding paragraph) (Asanoi, Sasayama et al. 1989).

The initial observations that lead up to the controversy as to whether the normal ventricle normally operates at the point of maximal efficiency or maximal SW merit explanation. The initial studies describing the relationship between stroke work and afterload had been done either in anaesthetized open chest animals, or using an isolated (excised) ventricle. In both of these preparations, the contractility is lower than in the normal physiological state (EF approximately 50% for the isolated ventricle versus normal in which EF exceeds 60%). Circulating catecholamines are present in the in vivo situation, and the compensatory reflexes of the intact cardiovascular system are responsible for inducing rapid adaptation via the adrenergic system (Fourie, Coetzee et al. 1992; Burkhoff and Sagawa 1986; Piene and Sund 1982). Furthermore, contractility may be decreased by anesthetic agents (Asanoi, Sasayama et al. 1989; Sagawa, Maughan et al. 1988).

Therefore the relationship between Ea and Ees can be classified into three broad coupling patterns:

1. Ees = 2Ea
2. Ees = Ea
3. Ees < Ea

Ea "line" in Figure 1.5.2.10	Ees/Ea	Matched to deliver:	Ejection Fraction: (LV) #	Contractility
1.	Ees = 2Ea	Maximum Efficiency	> 60 %	Normal state of left and right ventricles
2.	Ees = Ea	Maximum Stroke Work	59 to 40 %	Moderately depressed ventricle
3.	Ees < Ea	Neither efficiency nor stroke work	< 40 %	Failing ventricle

Table 1.5.2.1. The relationship between Ea and Ees. Adapted from (Fourie, Coetzee et al. 1992a; Fourie, Coetzee et al. 1992b; Asanoi, Sasayama et al. 1989; Kass and Maughan 1988; Sunagawa, Maughan et al. 1985). # No EF data for the RV exists.

1. The normal ventricle and loading conditions

During normal physiology, the right (Coetzee and Fourie 1993) and left (Myhre, Johansen et al. 1986) ventricle and their respective afterloads are optimally matched with respect to efficiency. Therefore, their working points lie on the peak of the efficiency versus afterload curve, and on the ascending limb of the stroke work versus afterload curve. Ventricular elastance is at least double arterial elastance. (This scenario corresponds to condition 1 in Table 1.5.2.1 and in Figure 1.5.2.10).

The normal ventricle operates at 90% of the maximal stroke work available for a particular Ees (Sagawa, Maughan et al. 1988). This confers an advantage on the ventricles, in that there is normally some reserve in terms of work (Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992b; Fourie 1989).

If the right and left ventricles are compared (Figures 1.5.2.7, 1.5.2.8 and 1.5.2.9), the shape of the curves of efficiency and work versus afterload are similar, but the absolute values of Ea and Ees are lower for the right ventricle than for the systemic side of the circulation. Therefore the power that the right ventricle can generate is much lower than that able to be generated by the left ventricle. Burkhoff and Sagawa indicate that stroke work and efficiency in a weaker ventricle are more sensitive to changes in afterload than in a stronger ventricle (Burkhoff and Sagawa 1986). These last two statements imply that the right ventricle with its smaller muscle mass and inherently lower Ees, possesses less reserve to accommodate acute rises in Ea.

2. The mildly depressed ventricle, or the ventricle facing an acute rise in arterial elastance

The priority of the mildly depressed right or left ventricle is to generate maximal work, and such a ventricle has been shown to operate at the peak of the stroke work versus Ea curve (Asanoi, Sasayama et al. 1989). This is at the cost of efficiency! This scenario can also apply when the afterload to the right (Bolliger, Fourie et al. 1991) or left ventricle acutely increases so that Ea and Ees become equal. Therefore when Ea = Ees, stroke work generated by the ventricle is maximal, and correlates with a LV ejection fraction of between 40 to 59% (Asanoi, Sasayama et al. 1989; Burkhoff and Sagawa 1986). No data for RVEF in this situation have as yet been described.

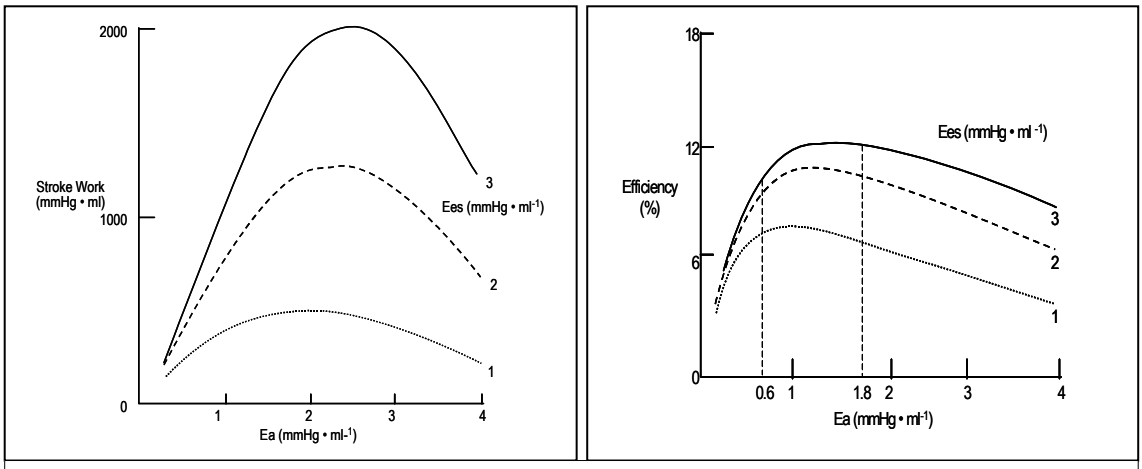


Figure 1.5.2.8. (Left hand diagram) Relationship between right ventricular stroke work and Ea for various values of Ees.
Figure 1.5.2.9. (Right hand diagram) Relationship between efficiency and Ea for various values of Ees for the right ventricle.

Both of these diagrams represent theoretical plots constructed using equations 1.5.4 and 2.9.3 inputted into the equation that describes ventricular efficiency, Efficiency = PVA/MVO_2. PVA was calculated from the product of end systolic pressure and stroke volume. To reconstruct these graphs, Ees was set in equation 1.5.4 as the independent variable at 1, 2 and 3 $mmHg.ml^{-1}$, and mean pulmonary artery pressure was varied between 0 to 50 mmHg. Compliance, Rp and Ea were varied as a function of mean pulmonary artery pressure according to regression analysis with mean PAP as the independent variable. Compliance = (-1.682 + 80.564)/mean PAP where r = 0.657, n =10. Rp = 0.646 + 0.06 mean PAP (r = 0.566, n =55). Redrawn from Fourie, Coetzee et al, 1992

From inspection of Figures 1.5.2.8, 1.5.2.9 and 1.5.2.10, it is evident that:

- Efficiency is more sensitive than stroke work to increases in Ea (Sagawa, Maughan et al. 1988; Burkhoff and Sagawa 1986) and decreases to 70% of maximal if Ea and Ees are equal (Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992a; Maughan 1988; Sagawa, Maughan et al. 1988; van den Horn, Westerhof et al. 1985) and,
- The afterload at which stroke work reaches its maximum occurs at about double the Ea value at which maximal efficiency occurs (Sagawa, Maughan et al. 1988).

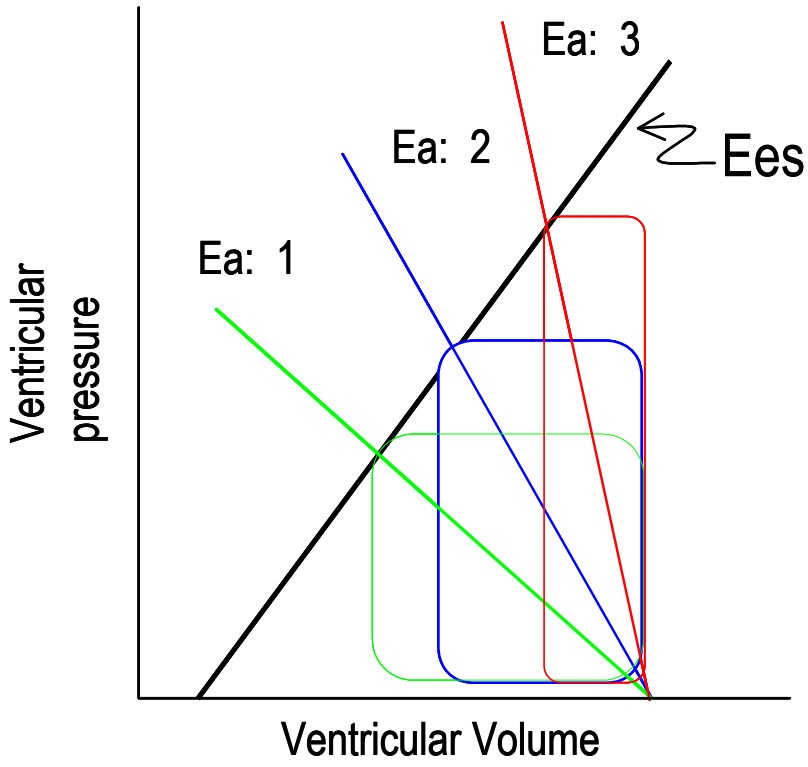


Figure 1.5.2.10. Schematic representation of ventricular-arterial coupling. A pressure-volume relationship is superimposed on the diagram. Three Ees / Ea relationships are illustrated:

1. Ea = Ees/2
2. Ea = Ees
3. Ea > Ees

Adapted from Asanoi, Sasayana et al, 1989 and Fourie, Coetzee et al, 1992.

3. The failing ventricle

Should either the load increase further, or the Ees decrease to the point where Ea > Ees, both efficiency and stroke work are on the declining slope of their curves: any further increase in Ea will cause them to decline markedly. A mismatch now exists between ventricular and arterial elastances (Asanoi, Sasayama et al. 1989). This is the definition of a failing pump, and corresponds to the right hand descending limbs in Figures 1.5.2.1, 1.5.2.2, 1.5.2.3, 1.5.2.6, 1.5.2.7, 1.5.2.8, 1.5.2.9 and 1.5.4.4. Ejection fraction for a left ventricle performing under such conditions is less than 40% (Asanoi, Sasayama et al. 1989).

1.5.3 The coupling of the right ventricle to the pulmonary circulation

Coupling of the RV to its load has only been described by Fourie at al (Fourie, Coetzee et al. 1992b). Maximum RV efficiency in intact pigs anaesthetized with 0.5% halothane occurred at an Ea of 1 mmHg.ml^{-1} and RVSW peaked at an Ea of 2 mmHg.ml^{-1}. Any further increases in Ea resulted in a decrease in stroke work with the right ventricle

starting to operate as a pressure pump (Fourie, Coetzee et al. 1992b). At the point of maximal efficiency, the Ees / Ea ratio was 1.7. As discussed above, maximal efficiency has been shown to occur at an Ees/Ea ratio of 2. Thus, the intact right ventricle subjected to 0.5% halothane anesthesia, operating against its normal load, operates close to optimal efficiency rather than as an optimally matched system operating at maximal SW (Fourie, Coetzee et al. 1992b; Piene and Sund 1982). That there is a move from 2 to 1.7 may reflect a decrease in Ees due to the depressant effects of halothane. Furthermore, Ea in the pulmonary artery of normal intact pigs has been reported to be 0.6 mmHg.ml^{-1}. This confers considerable reserve on the normal RV: if Ees remains constant, Ea could double before stroke work decreased (Fourie, Coetzee et al. 1992b).

Piene and Sundt investigated the coupling between the RV and the PA in an isolated preparation and concluded that the RV operates at maximal SW. Again, the difference in the results between these studies may lie therein that the Ees of the intact preparation is higher due to intact sympathetic nervous system (Fourie, Coetzee et al. 1992b; Sagawa, Maughan et al. 1988; Piene and Sund 1982).

Ea (mmHg.ml^{-1})	Mean PAP (mmHg)	Ees/Ea
1	15-20	Maximal efficiency; Ees = 1.7 Ea
1.6	20-30	
2	30-40	Maximal stroke work; Ees = Ea

Table 1.5.3.1 Coupling of right ventricle with Ees approximately 2 mmHg.ml^{-1} and its load. The pulmonary artery pressures associated with various Ea/Ees ratios (Fourie, Coetzee et al. 1992b).

1.5.4 Right ventricular-pulmonary artery interaction and compliance of the pulmonary vasculature

An extreme way of looking at looking at of ventricular-vascular interaction is that the heart could not function if the pulmonary artery were not compliant. During systole, the mitral valve is shut and if the PA was not able to store the stroke volume, the right ventricle would not be able to eject (Grant and Lieber 1996). Thus, the very compliant pulmonary vasculature serves as an impedance-uncoupling element between the ventricle and the peripheral vasculature where the major part of the resistance is located. Uncoupling results in a reduction of both input impedance and of the work done by the ventricle to generate pulsatile flow (Piene and Hauge 1976). However, RV performance is not completely independent of the PVR, as the ventricle still has to overcome

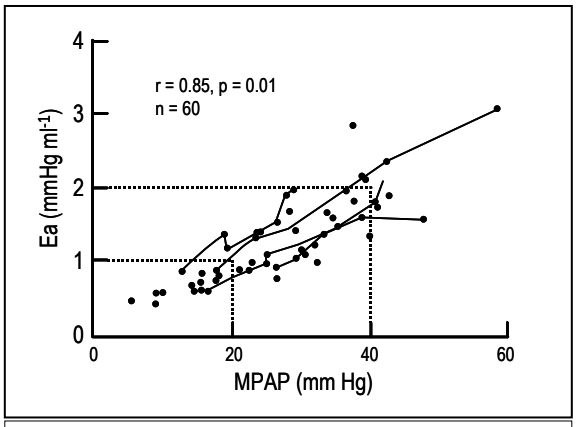


Figure 1.5.4.1. The linear relationship between Ea and mean pulmonary artery pressure. Redrawn from Fourie, Coetzee et al, 1992

pulmonary artery diastolic pressure for ejection to begin. The diastolic decline in pressure is related to the time constant. This time constant is governed by the product of peripheral resistance and compliance of the pulmonary vasculature (Fourie 1989).

Furthermore, the end of RV ejection does not correlate well with maximal RV elastance (E_{max}), as is the case for the left ventricle. This is a result of the balance between the compliant and resistive properties of the pulmonary vasculature (Piene 1986; Piene and Sund 1980). At higher resistance and low compliance values, as is the case in the systemic circulation, the end of ejection coincides more closely with the end of systole. At low resistance and high compliance as occurs in the pulmonary circulation, RV ejection is prolonged. It may present a mechanical advantage to the right ventricle to continue to deliver its stroke volume during diastole (Piene 1986). Nonetheless, Piene also commented that the optimal compliance of the PA might be lower than what is needed for the efficient systolic delivery of the stroke volume (Piene 1986). Pulmonary artery compliance should not be too low. A "moderate" compliance is the ideal. A "moderate compliance" will prevent blood accumulating during systole, but also avoid the other extreme of excessive opposition to RV ejection.

The relationship between the compliance of the pulmonary vasculature and RV-PA coupling has been described mathematically (Fourie, Coetzee et al. 1992b). From equation 1.4.4.12, it can be seen that both pulmonary vascular compliance and resistance affect impedance (Ea). The influence of PA compliance on Ea is complex. Fourie studied the interaction of compliance and resistance on RV-PA coupling (Fourie 1989). He showed that increases in resistance resulting in an increase in pulmonary artery pressure from 5 to 45 mmHg, caused a 56% decrease in stroke volume. It could be determined that the decrease in compliance contributed only 12% to the decrease in stroke volume. Therefore the decrease in compliance had a lesser effect on stroke volume than resistance (Fourie 1989). Studies conducted by both Piene and Sundt (Nozawa, Cheng et al. 1994) and Elzinga et al. (Piene and Sund 1979) are in accordance with these results. They used an isolated cat heart preparations pumping into an artificial load (i.e. a windkessel hydrodynamic circulatory model). They subjected the right ventricle of these preparations to increases in peripheral resistance and decreases in compliance. Both the resistance and the compliance changes produced decreases in stroke volume. However, the right ventricle appeared more sensitive to changes in resistance than compliance (Figure 1.5.4.2). The relationship between PAP, compliance and coupling of the RV to its load has also been studied by Piene and Hague (Piene and Hauge 1976). Working from a state of maximal vasodilatation, they demonstrated that moderate increases in pulmonary artery pressure produced by an increase in blood flow, caused dilation of the large pulmonary arteries. The increase in radius and therefore decrease in resistance induced by this manoeuvre outweighed the decrease in compliance. The nett result was a decrease in PA input impedance (Piene and Hauge 1976).

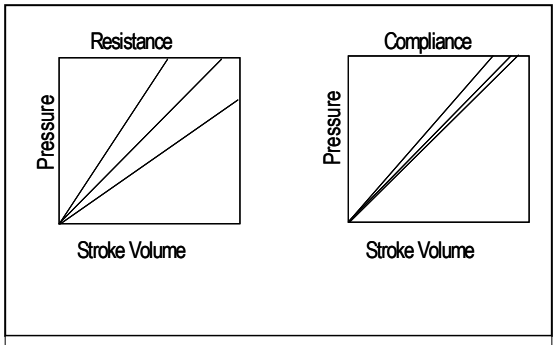


Figure 1.5.4.2 Pes-SV relationship. The slope of the Ea line changes markedly with changes in resistance but little with changes in compliance. Adapted from Sunagawa, Maughan et al, 1983

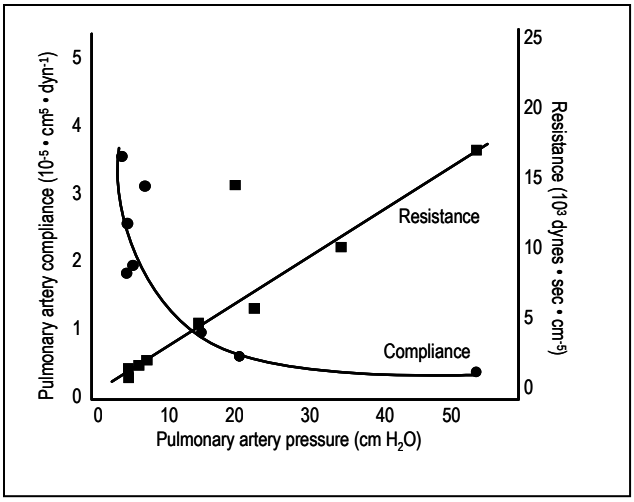


Figure 1.5.4.3

The effects of vasoconstriction on PA compliance.

Note the exponential decline in compliance that occurs as PVR and PAP increase.

Redrawn from Piene and Hauge, 1976

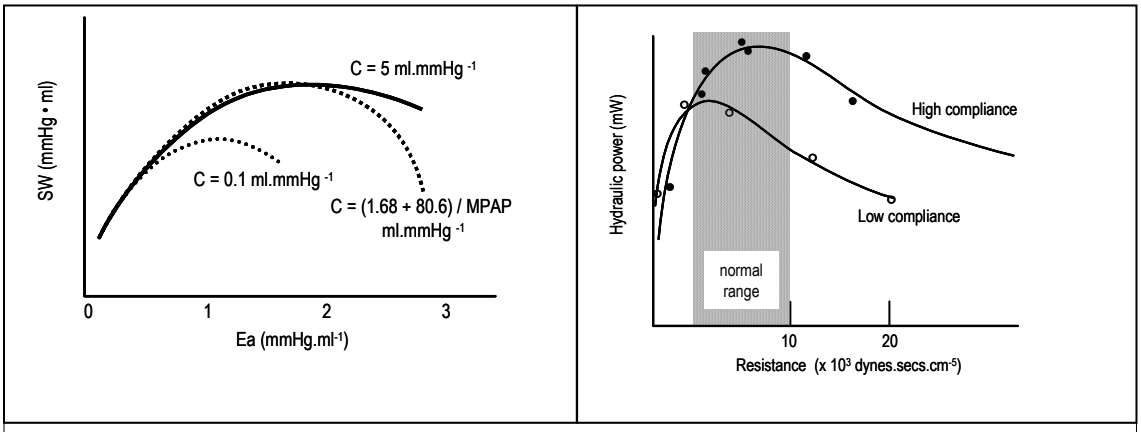


Figure 1.5.4.4. Two diagrams illustrating the effect of changes in PA compliance on the power output or work performed by the RV as opposition to pulmonary flow changes.

Left hand diagram: Redrawn from Fourie, 1989. The RV power output of the isolated cat heart (top) and the intact pig heart (bottom) versus elastance at high and low compliances. The relationship between SW and Ea where compliance is described as a function of mean PAP ((-1.682 + 80.564)/mean PAP) was derived from a non-linear regression model described for the porcine pulmonary vascular bed subjected to glass bead embolism by Fourie (Fourie 1989). The plot illustrating this relationship would be representative of what happens in the normal pulmonary vascular bed of pigs as the Ea changes between approximately 0 to 3 mmHg.ml^{-1}. The other relationships in this diagram illustrate the effects of significant increases or decreases in compliance on the generation of SW for a range of elastances.

Right hand diagram: Redrawn from Piene, 1987. The bottom diagram is a simplified rendition of the relationship between hydraulic power generation and resistance in the feline pulmonary vascular bed as compliance is varied. This diagram was published in a review entitled "Matching between right ventricle and the pulmonary bed" in the reference work, Ventricular/Vascular coupling edited by Frank Yin (Yin 1987). In this diagram, Piene has simplified previous work by himself and Sundt (Piene and Sundt 1979) to illustrate only relationships at the extremes of compliance that he tested. There is 10-fold difference between the maximal and minimal compliance (5 to 0.5 x 10^5 dynes.cm^{-5}) in this experiment. Note that hydraulic power is the product of pressure and mean flow.

If compliance affects opposition to pulmonary flow, it must affect the relationship between the work versus load relationship. A decrease in PA compliance has been shown to shift the relationship between stroke work and Ea down and to the left (Fourie, Coetzee et al. 1992b; Piene 1986) (Figure 1.5.4.4). A shift the curve down and to the left will result in the RV prematurely changing from the normal flow generator to a pressure pump situation with a decrease in the work done against a particular load (Fourie 1989). This is in keeping with the observations of Piene that the high compliance of the lung vasculature facilitates transfer of energy from the ventricle to the load (Piene 1986). Therefore although compliance plays a lesser role in determining Ea and stroke volume than Rp, it plays an important role in determining the coupling of the right ventricle to its arterial load (Fourie 1989).

1.5.5 Consequences of ventricular-arterial coupling on right ventricular pump characteristics

The right ventricle normally operates on the ascending limb of the power-load curve (Fourie 1989; Piene 1986; Pouleur, Lefevre et al. 1978). If the diagrams depicting the relationships between power and afterload are inspected (Figures 1.5.4.4 and 1.4.1-f), it is apparent that the ascending limbs of these relationships approximate a straight line and can be described by the equation that describes a "flow pump":

Power = "afterload" x flow^2 …… Equation 1.5.5.1

Where

"Afterload" is a variable describing opposition to pulmonary flow. This opposition to pulmonary flow has been described by arterial elastance, characteristic impedance or resistive properties of the pulmonary vascular bed (Fourie 1989, Fourie, Coetzee et al. 1992, Piene 1986).

That the RV normally operates as a flow pump was originally deduced by work done by Pouleur et al. (Piene and Sund 1979). They demonstrated that elevation of characteristic impedance due to clamping of the left pulmonary artery caused peak ventricular and pulmonary artery pressures to increase. This manoeuvre resulted in an increase in the hydraulic power output of the right ventricle. The increase in RV power output in the face of an increase in impedance led Pouleur to conclude that this ventricle operates, under normal circumstances, as a low-pressure high-volume flow pump. This scenario is usually abbreviated to the term "flow generator" (Fourie, Coetzee et al. 1992; Fourie 1989).

The implication of the RV operating on the ascending part of the SW-elastance relationship is that it possesses sufficient reserve to overcome the small day-to-day physiological changes in opposition to RV ejection. The reserve is such that the opposition to RV ejection must double before the right ventricle tops the summit of the work versus load curve and starts operating as a pressure pump (Fourie, Coetzee et al. 1992).

However, the descending limb of the power-afterload relationships have a different form and are described by the following relationship:

Power = P^2 / "afterload" …… Equation 1.5.5.2

Where

"Afterload" is a variable describing opposition to pulmonary flow, for example effective arterial elastance, characteristic impedance or resistance (Fourie 1989, Fourie, Coetzee et al. 1992, Piene 1986).

This equation describes a hyperbola with the slope equal to the inverse of the parameter describing afterload (Fourie 1989; Piene 1986). When the RV works on this part of the power versus afterload curve, it operates as a constant pressure, variable output generator. In this situation, the pressure generated by the RV will be little altered by changes in resistance. The reason for this is that if resistance decreases, pressure will be maintained by an increase in flow and vice versa (Fourie, Coetzee et al. 1992; Fourie 1989; Piene 1986).

Before classifying the ventricle as a pressure pump or flow generator, it is important to know the working point on the power-load curve (Piene 1986, Fourie 1989). The point of maximum power transfer occurs where the two curves described by equations 1.5.5.1 and 1.5.5.2 intersect on the power-afterload graph (Fourie, Coetzee et al. 1992; Fourie 1989). At this point, arterial and ventricular elastances are numerically equal and maximal SW is generated. Therefore when the ventricle and its afterload operate at a point where Ea is equal to or less than Ees, the right ventricle will operate as a flow generator. When the load increases so that Ea exceeds Ees, the RV makes the transition from operating as a flow generator to now operating as a pressure pump. A ventricle and its load operating on the latter position on the power-afterload relationship is, per definition, failing. In a porcine model of pulmonary bead embolism, Fourie determined that the RV makes the transition from flow to pressure generator and fails as a pump when Ea reaches 2 $mmHg.ml^{-1}$ (Fourie 1989). An Ea of 2 $mmHg.ml^{-1}$ corresponds to a mean pulmonary artery pressure of 30 to 40 mmHg in both humans and animals (Fourie, Coetzee et al. 1992b, Vlahakes, Turley et al. 1981, Sibbald and Driedger 1983). The pathophysiological consequences of RV failure due to an increase in afterload will be dealt with in the next section.

1.6 Pathophysiological consequences of an acute increase in right ventricular afterload

As long ago as 1936, Fineberg and Wiggers while studying the consequences of pulmonary vascular obstruction, demonstrated insight by stating that "*the right ventricle has only limited power of response to a drastic sudden increase in pulmonary vascular resistance, and that fatigue and failure easily supervene when aortic pressure, and with it coronary flow, is suddenly reduced…. It is easy to understand why a circulatory crisis may be brought about through failure of the right ventricle…*" (Hurford and Zapol 1988).

Right ventricular enlargement due to a sudden increase in afterload of pulmonary vascular origin is termed acute Cor Pulmonale (Wiedemann and Matthay 1997; Schulman and Matthay 1992). This relatively thin-walled chamber possesses a limited reserve to cope with increases in afterload (Figure 1.6.1). When faced with even a modest (Dries and Mathru 1992) increase in afterload, many investigators have shown that right ventricular stroke volume and

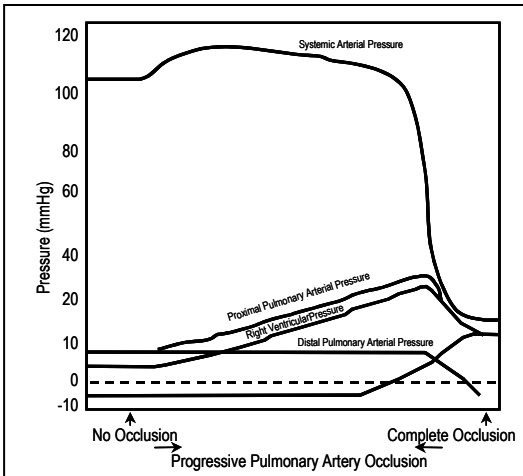


Figure 1.6.1. Guyton described the events as the main pulmonary artery of the dog is progressively constricted over a 5-minute period. Initially RV pressure progressively increased, and cardiac output was maintained. However, when systemic pressure dropped below a mean of 40 to 60 mmHg, progressive and rapid collapse of the circulation occurred within 6 to 10 minutes. The pulmonary artery constriction decreased filling of the LV via decreased right ventricular stroke volume. Adapted from Guyton, Lindsey et al, 1954

ejection fraction decrease (Figure 1.6.2.1) (Dries and Mathru 1992; Calvin, Jr. 1991; Calvin, Jr., Baer et al. 1985; Weber, Janicki et al. 1983; Sutherland, Calvin et al. 1981; Piene and Sund 1979). These decreases in RV output are inversely proportional to the increase in mean pulmonary artery pressure (Figure 1.6.2.1) (Brunet, Dhainaut et al. 1988; Sibbald, Driedger et al. 1983). The normal right ventricle can generate maximum pulmonary artery pressures of 40 mmHg mean or pressure of 60 to 70 mmHg systolic without pharmacological support (Reuse, Frank et al. 1988; Weber, Janicki et al. 1983). A hypertrophied right ventricle may tolerate a larger rise in afterload, at the expense of a high end-diastolic pressure (Dries and Mathru 1992; Schulman and Matthay 1992). The discussion that follows deals predominantly with an inexperienced and non-hypertrophied right ventricle facing an acute increase in afterload (Figure 1.6.1).

1.6.1 The increase in RVEDV

An increase in RVEDV in the presence of an increased afterload is a part of the definition of cor pulmonale. An increase in EDV comprises an important compensatory mechanism of the afterloaded RV in order to maintain its stroke volume and increase its stroke work (Figure 1.6.2.2) (Hendry, Ascah et al. 1994; Mitsuo, Shimazaki et al. 1992; Dries and Mathru 1992; Schulman and Matthay 1992; Calvin, Jr. 1991; Dhainaut, Lanore et al. 1988; Brunet, Dhainaut et al. 1988; Sibbald, Driedger et al. 1983; Milnor 1982c; Guyton, Lindsey et al. 1954; Schulman and Matthay 1992; Hendry, Ascah et al. 1994). The increase in EDV is proportional to the rise in pulmonary artery pressure (Brunet, Dhainaut et al. 1988; Sibbald, Driedger et al. 1983) and may, within certain limits, be augmented by volume therapy (Dries and Mathru 1992; Guyton, Lindsey et al. 1954). Because of the high diastolic compliance of the right ventricle, the RVEDP remains low and increases slowly until dilation of the right ventricle is limited by the pericardium (Hurford and Zapol 1988; Janicki and Weber 1980; Maughan, Shoukas et al. 1979). Therefore the initial right ventricular response to an increase in opposition to RV ejection is dilatation rather than an increase in EDP (Hurford and Zapol 1988). For example, on embolization of the pulmonary microvasculature of dogs with glass beads during which the mean pulmonary artery pressure increased from 14 to 48 mmHg, RVEDV increased from 91+/- 8 to 131 +/- 15 ml, while RVEDP increased only from 4 to 8 mmHg (Hurford and Zapol 1988). Stool et al. demonstrated another example of this great RV compliance (Stool, Mullins et al. 1974). Their experimental model included the inflation of a balloon in the

PA. At the point of maximal right ventricular pressure generation (100 mmHg systolic and 60 mmHg mean), RVEDP averaged only 10 mmHg (Stool, Mullins et al. 1974).

Only when the limits imposed by the inelastic pericardium are reached do further increases in RVEDV than described above results in significant increases in RVEDP (Calvin 1991; Calvin, Jr. 1991; Vlahakes, Turley et al. 1981). Glantz et al. (Glantz, Misbach et al. 1978) have demonstrated that with the pericardium open, the thin walled right ventricle can undergo substantial dilatation with only small increases in EDP. Hurtford and Zapol suggest that the ability of the right ventricle to compensate for acute rises in pulmonary artery pressure may be physically limited by the surrounding pericardium (Hurford and Zapol 1988).

1.6.2 Ventricular interaction during pulmonary hypertension

The various forms of ventricular interaction play a major role in influencing global cardiac function when right ventricular afterload increases. The rise in intrapericardial pressure that results, accentuates the normal parallel interaction between the ventricles (Vlahakes, Turley et al. 1981). Firstly, external pressure is exerted on the left ventricle that affects its ability to distend. This has been likened to intrapericardial tamponade of the LV by the right ventricle as they compete for space within the pericardial sac (Wiedemann and Matthay 1997; Calvin 1991; Milnor 1982c; Spotnitz, Berman et al. 1971; Calvin 1991)

A second effect is that marked septal shift occurs in the presence of pulmonary hypertension (Figures 1.6.2.3 and 1.6.2.4) (Weber, Janicki et al. 1983; Kingma, Tyberg et al. 1983). An increase in right ventricular diastolic pressures will result in a decrease or even reversal in the transseptal diastolic pressure gradient. Kingma et al. (Kingma, Tyberg et al. 1983) have studied the relationship between the diastolic transseptal pressure gradient and the position of the septum. When the gradient is low or reversed, the interventricular septum shifts leftward at the end of diastole. Diastolic septal shift is termed paradoxical motion of the septum (Kingma, Tyberg et al. 1983).

Septal shift causes left ventricular geometry to become distorted. Distortion of the LV results in a decrease in diastolic compliance with the left ventricular diastolic pressure-volume relationship being shifted upward and to the left (Figure 1.3.5.1) (Calvin 1991; Calvin, Jr. 1991; Hurford and Zapol 1988; Weber, Janicki et al. 1983; Vlahakes, Turley et al. 1981; Sutherland, Calvin et al. 1981). Consequently there is a poor correlation between pulmonary artery wedge pressure and cardiac index in pulmonary hypertension (Martyn, Snider et al. 1981). A decrease in LV compliance results in LV under-filling. Stool et al. have showed that LV volume progressively decreased when mean pulmonary artery pressures were greater than 30 mmHg, and at 60 mmHg, LVEDV was reduced by 30% (Stool, Mullins et al. 1974). This under filling leads to a decrease in LV stroke volume. A compensatory baroreceptor-mediated increase in sympathetic nervous system stimulation (SNS) occurs. SNS activation increases left and right ventricular contractility and induces a tachycardia that initially compensates for the circulatory dysfunction (Stool, Mullins et al. 1974; Guyton, Lindsey et al. 1954). When this compensatory mechanism is overwhelmed, systemic hypotension will worsen.

Hendry and colleagues propose an additional view of septal shift. They suggest that the septal shift encountered in pulmonary artery hypertension may hold an adaptive advantage in that the right ventricle has a larger EDV and therefore will generate a larger stroke volume (Hendry, Ascah et al. 1994).

In the face of a decreased right ventricular output, Calvin has repeatedly shown that the LV is underfilled. This occurs even if no septal shift has taken place. It is an example of a series interaction of the two ventricles (Calvin 1998; Calvin, Jr. 1991; Calvin and Quinn 1989).

1.6.3 Right ventricular ischemia during acute pulmonary hypertension

RV ischemia with ischemic dysfunction of the right ventricle completes the pathophysiological viscous circle illustrated in Figure 1.6.5.1 (Hurford and Zapol 1988; Vlahakes, Turley et al. 1981). When faced with an increase in afterload, both pressure and volume of the ventricle increase, and the wall stress of the RV rises. The reduction in wall thickness as the ventricle dilates, accentuates the rise in wall tension (Martyn, Snider et al. 1980). Increased systolic compression of the intramural coronary vessels during right ventricular hypertension decreases the perfusion pressure gradient between the aorta and the right ventricle. An increase in coronary blood flow can only then occur with

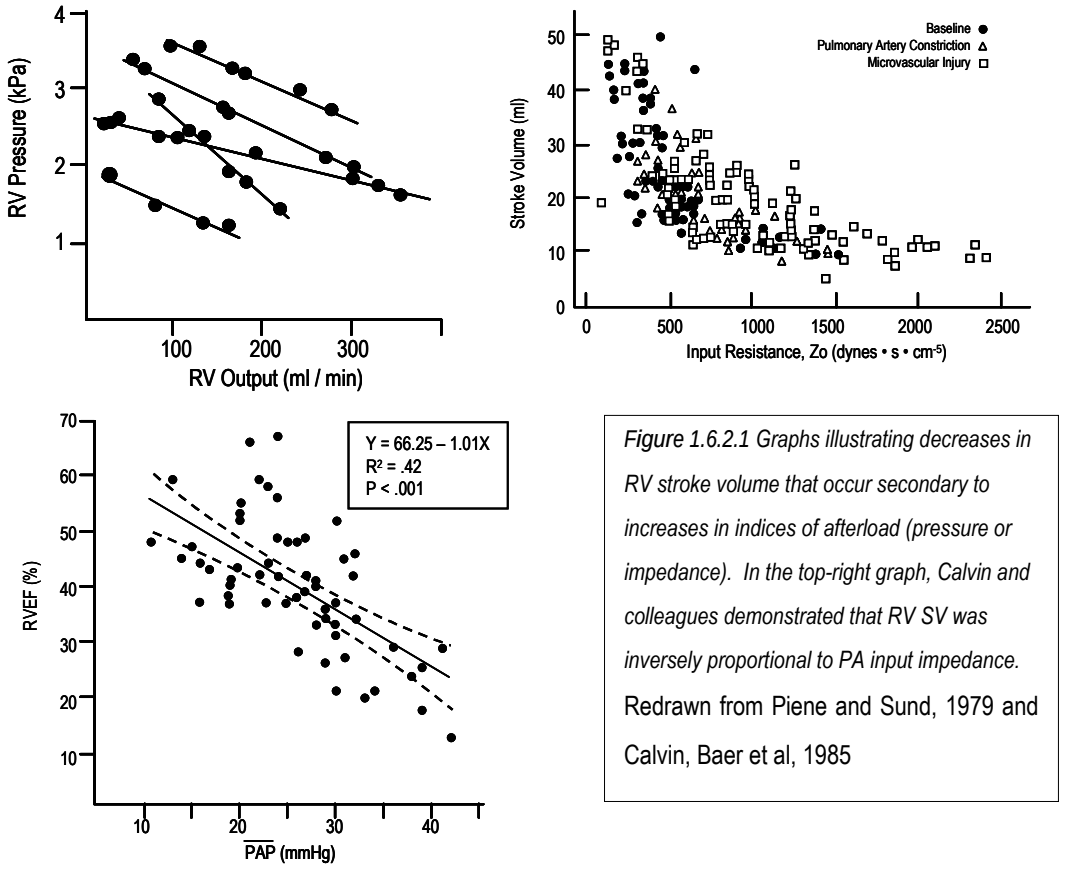


Figure 1.6.2.1 Graphs illustrating decreases in RV stroke volume that occur secondary to increases in indices of afterload (pressure or impedance). In the top-right graph, Calvin and colleagues demonstrated that RV SV was inversely proportional to PA input impedance. Redrawn from Piene and Sund, 1979 and Calvin, Baer et al, 1985

concomitant decreases in coronary vascular resistance or increases in coronary perfusion pressure (Gold and Bache 1982). The closer the right ventricular pressures are to systemic, the more the RV behaves like the LV in terms of coronary blood flow with the bulk of right ventricular coronary blood flow occurring during diastole (Dries and Mathru 1992; Gold and Bache 1982).

With moderate increases in right ventricular pressure, it has been repeatedly demonstrated that the coronary vascular reserve is sufficient to meet the increase in demand for oxygen (Wiedemann and Matthay 1997; Dries and Mathru 1992; Calvin, Jr. 1991; Calvin and Quinn 1989; Gold and Bache 1982; Vlahakes, Turley et al. 1981; Manohar, Tranquilli et al. 1981). Manohar and colleagues have demonstrated that coronary blood flow increased by 91 % when the RV was faced with an increase in afterload, even if aortic pressure decreased by 15 mmHg (Manohar, Tranquilli et al. 1981). Gold and Bache demonstrated that when right ventricular systolic pressure was increased to *92 mmHg*, RV coronary blood flow increased by more than 200% (Gold and Bache 1982). Even though mean aortic pressure was unchanged at this stage of the study, the transmural distribution of blood flow indicated right ventricular subendocardial hypoperfusion, albeit coronary vasodilator reserve had not yet been exhausted (Gold and Bache 1982). The increase in work done by the RV plus the increase in RV wall stress lead to an increase in myocardial oxygen demand (Calvin, Jr. 1991). Calvin has confirmed that the aforementioned increases in CBF are indeed sufficient to meet the increased demand. He demonstrated the absence of biochemical evidence of ischemia at “moderate” levels of right ventricular pressure overload (Calvin 1998).

In spite of the above work demonstrating absence of RV ischemia, other authors suggest that with acute and severe increases in right ventricular afterload, right ventricular blood supply eventually fails to increase in proportion to demand (Vlahakes, Turley et al. 1981). When coronary vasodilatation is maximal and coronary vascular reserve is exhausted, any decrease in driving pressure will result in decreases in coronary blood flow. The onset of rapid circulatory collapse in various models at this point has repeatedly been shown to be related to RV ischemic dysfunction (Calvin and Quinn 1989; Gold and Bache 1982; Milnor 1982c; Vlahakes, Turley et al. 1981; Manohar, Tranquilli et al. 1981; Fixler, Archie et al. 1973; Spotnitz, Berman et al. 1971; Guyton, Lindsey et al. 1954). However, other investigators indicate that ischemia may not be necessary for RV failure to occur when it is faced with an increase in afterload.

Vlahakes, Turley and Hoffman described exhaustion of coronary vascular reserve during acute RV hypertension when the PA was constricted until maximal RV pressures (65 mmHg) were generated. The exhaustion of coronary vascular reserve (no hyperemia) was associated with the development of right ventricular ischemia and the onset of circulatory collapse. One question that has been asked is whether the point of circulatory collapse during acute pulmonary hypertension is associated with LV ischemia. To answer this question, Vlahakes and colleagues elegantly studied biochemical indicators of ischemia and coronary hemodynamics in both ventricles before, during and after the point of collapse. No evidence of LV ischemia could be elucidated at the point of circulatory collapse (Vlahakes, Turley et al. 1981).

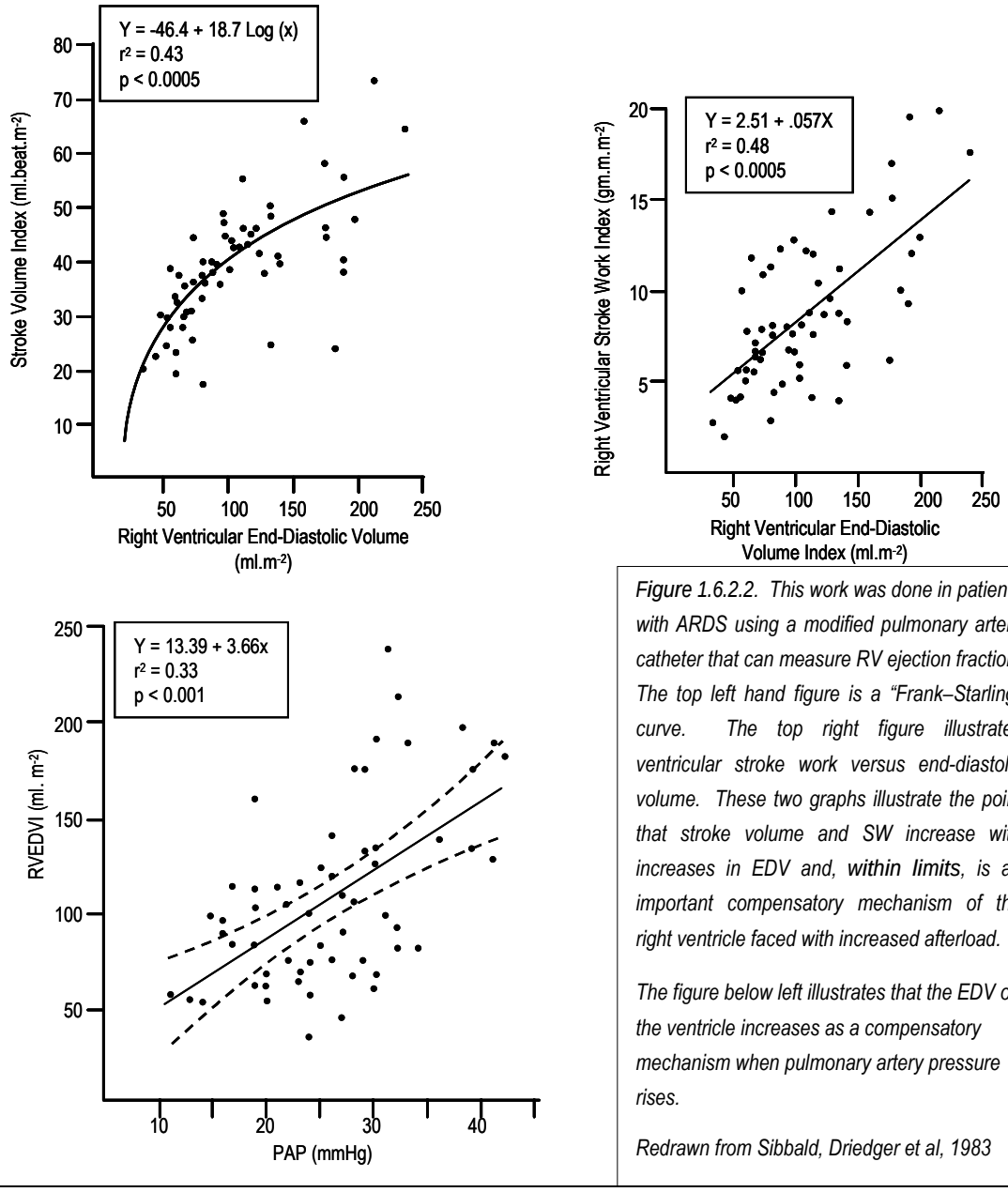


Figure 1.6.2.2. This work was done in patients with ARDS using a modified pulmonary artery catheter that can measure RV ejection fraction. The top left hand figure is a "Frank–Starling" curve. The top right figure illustrates ventricular stroke work versus end-diastolic volume. These two graphs illustrate the point that stroke volume and SW increase with increases in EDV and, within limits, is an important compensatory mechanism of the right ventricle faced with increased afterload.

The figure below left illustrates that the EDV of the ventricle increases as a compensatory mechanism when pulmonary artery pressure rises.

Redrawn from Sibbald, Driedger et al, 1983

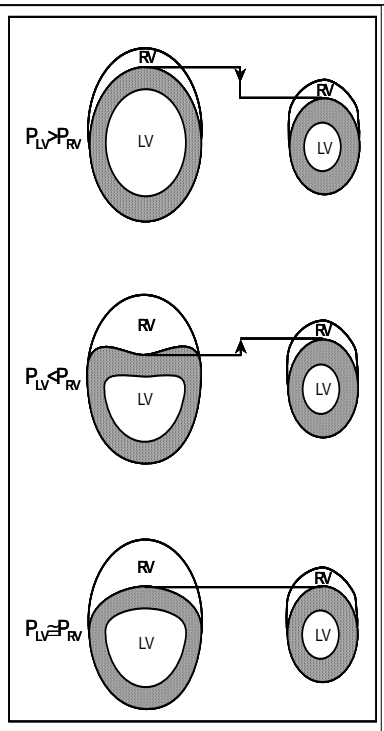


Figure 1.6.2.3 Left hand side represents the events during diastole; the right hand side represents the events during systole

Top: Normal situation: LV pressure exceeds RV pressure throughout the cardiac cycle. This causes the interventricular septum (IVS) to have a curvature similar to the LV in both systole and diastole.

Middle: When RV pressure exceeds LV pressure at the end of diastole, the IVS is displaced leftward and may actually become convex toward the LV. During systole, there is a rapid increase in LV pressure with restoration of a positive LV-RV pressure gradient. This causes the IVS to move toward the RV in a paradoxical direction as it resumes its normal convex curvature toward the LV. However, with severe rises in RV pressure, and large reductions in the normal systolic transseptal gradient, the IVS may remain deformed (shifted leftward) at the end of systole.

Bottom: With reductions in the normal diastolic transseptal gradient, the septum moves toward a progressively more neutral position between the ventricles. Therefore, in situations where the right and left ventricular end-diastolic pressures are almost equal, IVS motion may be minimal, or move hypokinetically in any direction. Redrawn from Kingma, Tyberg et al, 1983

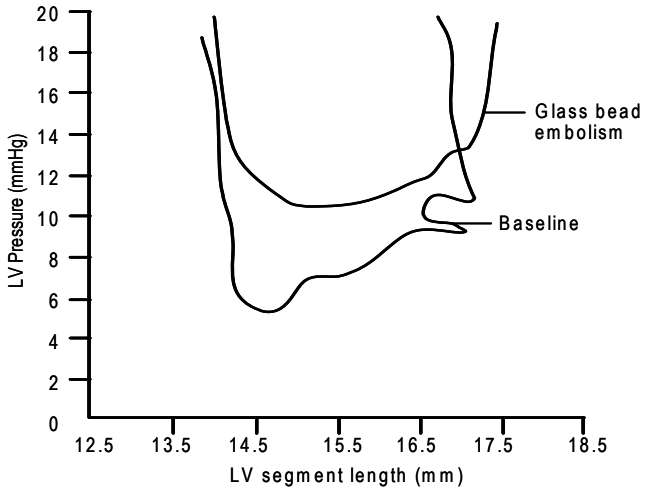


Figure 1.6.2.4 LV diastolic pressure length relationship before and after pulmonary hypertension. PHPT shifts the relationship up and to the left.

Redrawn from Calvin, 1991

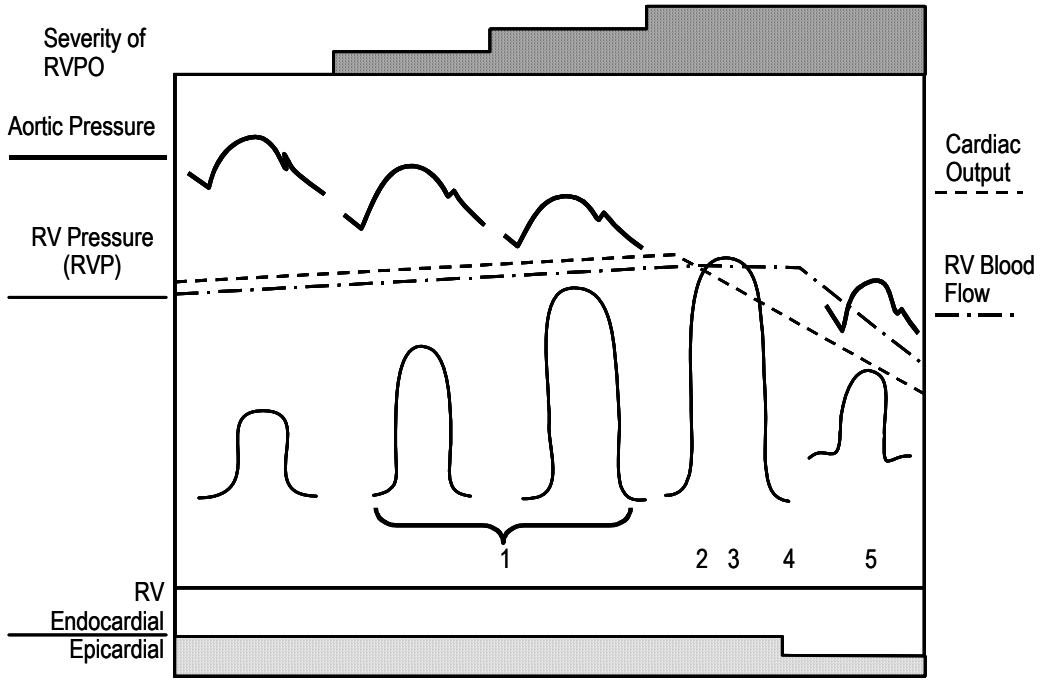


Figure 1.6.3.1 An integrated chronology of events leading to RV failure during RV pressure overload (RVPO) as formulated from a summary of the available evidence by Calvin and Quinn, 1989.

The black bars on the top indicate severity of the PVPO. The bars at the bottom indicate the RV endocardial to epicardial blood flow ratio.

Point 1. Moderate degrees of RV pressure overload are well tolerated without evidence of ischemia. Cardiac output is well maintained by increased inotropicity, heart rate and preload reserve. RV blood flow increases to meet the increased metabolic demands. The increase in CBF occurs even though the driving pressure for RV CBF is decreasing because of autoregulation of CBF.

Points 2 and 3. As RV afterload increases further, mismatch of the ventricle and its load occur and right ventricular stroke volume and cardiac out put decreases.

Point 4. Right ventricular ischemia develops beyond this point as demand starts exceeding the ability to supply oxygen. RV endocardial to epicardial ratio decreases at this point.

Point 5. When the right ventricle fails and systemic hypotension ensues, right ventricular ischemia leads to decreases in RV CBF, right ventricular systolic pressure generation, cardiac output and endocardial to epicardial ratios. Aortic pressure decreases from a combination of decreased left ventricular preload secondary to a decreased RV stroke volume (series interaction) and decreased compliance of the left ventricle, (parallel interaction). The decrease in aortic pressure further impairs right ventricular CBF by reducing the driving pressure: CBF is linearly dependent on the upstream pressure when the coronary bed is maximally dilated. This explains why increasing the systemic pressure can increase RV coronary blood flow but not at an earlier phase when the coronary bed may not be maximally dilated.

Calvin and Quinn, 1989

It is interesting to note the discrepancy between two investigations regarding right ventricular coronary vasodilator reserve. In the study already quoted above by Gold and Bache, further constriction of the PA to produce pulmonary artery pressures of 92 mmHg decreased myocardial blood flow to approximately baseline levels and the ratio of subendocardial to epicardial blood flow was reduced (Gold and Bache 1982). Albeit that mean aortic pressure at this point was 50 to 55 mmHg and the RVEDP had increased from 4 to 13 mmHg, they describe no exhaustion of the coronary vasodilator reserve (Hurford and Zapol 1988; Gold and Bache 1982). Maximal RV CBF during acute systolic overload increased flow to 1.69 ml.min^{-1}.gram^{-1}, and adenosine administration allowed up to 2.25 ml.min^{-1}.gram^{-1} of tissue in the dog myocardium. Vlahakes and co-workers described exhaustion of the coronary vasodilator reserve in acute PHPT; they suggest that the discrepancy is due to the *differing definitions of right ventricular failure* used in these studies (Vlahakes, Turley et al. 1981). Vlahakes et al. defined right ventricular failure by changes in RV and systemic pressures that continued to progress without further increments of PA constriction, whereas Gold and Bache used a definition comprising a decrease in aortic pressure and an increase in RVEDP (Gold and Bache 1982).

When the severity of RV dysfunction causes a decrease in aortic pressure, coronary perfusion pressure decreases further (Calvin, Jr. 1991; Hurford and Zapol 1988; Gold and Bache 1982). However, reversal of ischemic dysfunction has been demonstrated by improving RV coronary perfusion pressure, even if the increase in afterload is sustained (Hurford and Zapol 1988; Gold and Bache 1982; Milnor 1982c; Vlahakes, Turley et al. 1981; Guyton, Lindsey et al. 1954). In the study by Vlahakes et al, it is noteworthy that administration of adenosine increased CBF to even greater levels than did aortic constriction but adenosine did not restore function of the ventricle (Gold and Bache

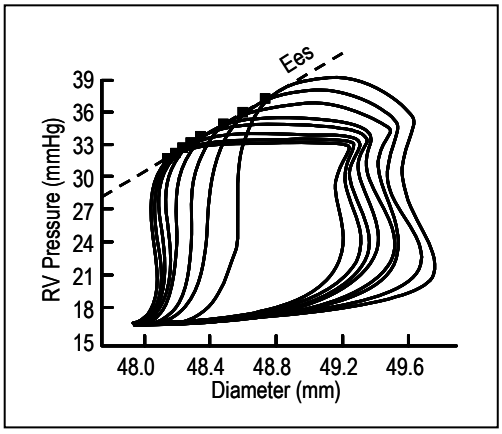


Figure 1.6.4.1 The diagram illustrates several right ventricular pressure length loops recorded while the afterload is being increased.

The slope end systolic pressure length relationship remains constant in the face of the increase in afterload. Note also the compensatory increase in pressure and segment length (volume) at the end of diastole in an attempt to maintain stroke volume.

Fourie, Coetzee et al, 1992.

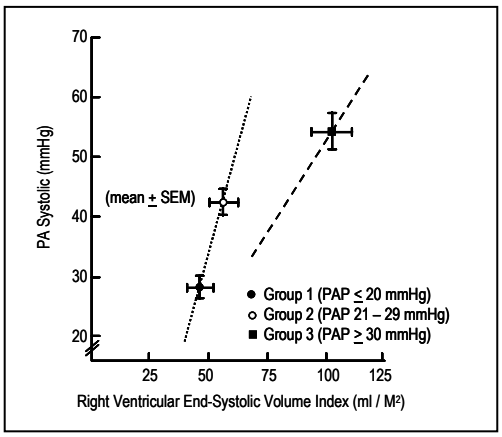


Figure 1.6.4.2. Peak ESPV points averaged from three groups of patients with pulmonary artery pressures in ARDS as indicated. The group with the highest PAP has its ESPV point shifted significantly over to the right. Sibbald and co-workers suggest that this implies that right ventricular contractile performance is reduced in patients with a mean PAP of more than 30 mmHg. This may however simply demonstrate the non-linearity of the ESPVR at the extremes of its range.

Sibbald, Driedger et al, 1983

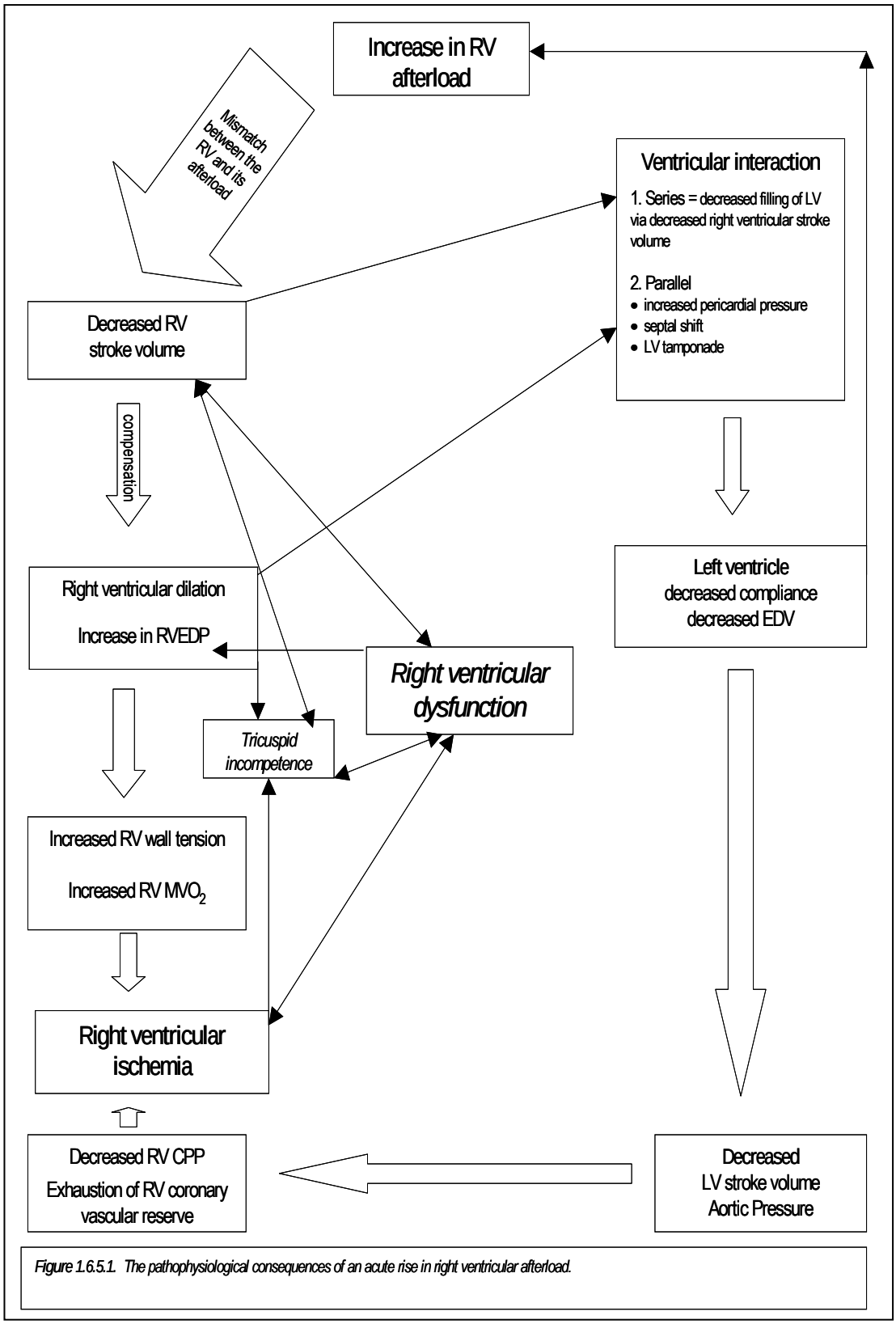


Figure 1.6.5.1. The pathophysiological consequences of an acute rise in right ventricular afterload.

1982). The difference was suggested to be due to the difference in the distribution of CBF generated by the two methods (Gold and Bache 1982). These authors do not discuss the influence that an increase in left ventricular pressure may have on ventricular-ventricular interaction, or on the LV contribution to RV pressure generation. Right ventricular contractility during acute pulmonary hypertension

1.6.4 Right ventricular contractility during pulmonary hypertension

The contractility of the right ventricle faced with an acute increase in afterload does not change. The RV Ees has been reported to be unchanged when faced with an increase in right ventricular afterload (Figure 1.6.4.1) (Fourie, Coetzee et al. 1992b; Fourie 1989; Brunet, Dhainaut et al. 1988; Sibbald, Driedger et al. 1983). LV contractility also appears unaffected by acute pulmonary hypertension (Hurford and Zapol 1988; Sibbald, Driedger et al. 1983). However, Sibbald and co-workers have suggested that patients with ARDS and mean pulmonary artery pressures of greater than 30 mmHg may exhibit a decrease in Ees (Figure 1.6.4.2) (Sibbald, Driedger et al. 1983).

1.6.5 The atrium during pulmonary hypertension

The interatrial septum may play a role in the pathophysiology of right ventricular afterload. A “probe patent” foramen ovale exists in 50% of people up to 5 years of age and 25% of persons older than 20 years of age. .

A potential left to right communication exists in 25% of adults if left atrial pressure exceeds right atrial pressure. Because it is less compliant than the right atrium, left atrial pressure is normally greater than right atrial pressure throughout systole. The pressure gradient and flow across a patent foramen ovale is greatly affected by factors that affect right ventricular compliance (Schwartzman, Attubato et al. 1993). A decrease in right ventricular compliance will increase right atrial pressure relative to that of the left atrium. This pressure gradient would facilitate shunting of deoxygenated blood across a patent foramen ovale. This has been demonstrated to be a cause of arterial hypoxemia in patients with acute increases in pulmonary artery pressure, right ventricular infarction and after pneumonectomy (Schwartzman, Attubato et al. 1993; Dries and Mathru 1992). The patent foramen ovale may provide a route for systemic embolization of other material during an increase in right ventricular afterload. Dilation and / or ischemia of the right ventricle may lead to tricuspid incompetence that may further decrease forward stroke volume (Dries and Mathru 1992).

1.7 One lung anesthesia and right ventricular function

The paucity of information on the interaction of the right ventricle and its afterload during one lung anesthesia has been commented on in the literature (Cohen 1995; Lewis-JW, Bastanfar et al. 1994). The effects of OLA on RV function will be examined.

1.7.1 Increases in right ventricular afterload during one lung anesthesia

1.7.1.1 Effects of one lung anesthesia (OLA) on right ventricular afterload

- Boldt et al, (Boldt, Muller et al. 1996) described an increase in pulmonary artery pressure after initiation of one lung anesthesia in patients undergoing both lobectomy (20.8 ± 2.5 to 27.2 ± 4.1 mm Hg) and pneumonectomy (21.1 ± 3.4 to 27.9 ± 3 mm Hg). They did not however, report any data describing pulmonary vascular resistance.

- Carlsson and colleagues (Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Carlsson, Bindslev et al. 1985) have investigated various aspects of one lung anesthesia (the use of various inhalation anesthetic agents (IAA's) and the effect of time on the HPV response) in humans. They have consistently demonstrated a 37 to 50% increase in pulmonary artery pressure compared to control, a doubling of PVR in the non-dependent lung, but no change in PVR of the dependent lung.

- Malmkvist and colleagues (Malmkvist, Fletcher et al. 1989; Werner, Malmkvist et al. 1984; Werner, Malmkvist et al. 1984) studied 17 patients with chest wall or small intrapulmonary lesions who had only minor abnormalities in lung function and would therefore have had normal perfusion to both lungs preoperatively. They described an increase in mean pulmonary artery pressure during one lung anesthesia from 17 $\pm$ 5 to 19 $\pm$ 6 mm Hg. No values for pulmonary vascular resistance were described. No significant relationship between cardiac index and pulmonary artery pressure was found. However, a significant relationship between pulmonary artery pressure and pulmonary shunt fraction during one lung anesthesia was found (Figure 1.7.1.2).

- Fujita and colleagues (Fujita, Yamasaki et al. 1993) studied the suitability of using sevoflurane for one lung anesthesia in healthy sheep. During one lung anesthesia with ZEEP or $PEEP_5$ to the dependent lung, pulmonary artery pressures did not change, but on the application of $PEEP_{10}$ to the dependent lung, pulmonary artery pressures (systolic/diastolic) increased from baseline 23/13.6 to 24.5/15.6 mm Hg. From their results, it can be calculated that PVR did not change during one lung anesthesia during ZEEP, $PEEP_5$ or $PEEP_{10}$. Increases in pulmonary artery pressure such as those described by Fujita and colleagues and Malmkvist and colleagues are clinically insignificant.

- Inomata and colleagues studied humans with normal preoperative lung function tests (Inomata, Nishikawa et al. 1997). They demonstrated that PVR did not change when ZEEP (208 $\pm$ 64 dynes.sec.cm^{-5}.m^{-2}) or up to 7.8 cm H_2O PEEP (220 $\pm$ 58 dynes.sec.cm^{-5}.m^{-2}) was applied to their dependent lungs. However, if an additional 6.5 cm H_2O PEEP was applied to the dependent lung, pulmonary vascular resistance increased to 286 $\pm$ 109 dynes.sec.cm^{-5}.m^{-2}. Although this rise in PVR is statistically significant, the clinical significance of this increase in PVR is uncertain. Pulmonary artery pressures were however not reported in their study.

- Cohen and co-workers (Cohen, Eisenkraft et al. 1988) conducted a systematic study of hemodynamics during one lung anesthesia while ZEEP or $PEEP_{10}$ was applied to the dependent lung and/or $CPAP_{10}$ to the non-dependent lung. The 20 patients studied were chosen because they had no significant pulmonary or cardiovascular disease. Neither mean PAP nor PVR differed during any measurement epoch (2 lungs on side, one lung anesthesia, $PEEP_{10}$, $PEEP_{10}$/$CPAP_{10}$ or $CPAP_{10}$). In other studies conducted by Cohen's group (Cohen and Eisenkraft 1996; Cohen, Thys et al. 1985a), no change in mean PAP (or PVR where reported) was described on initiation of one lung ventilation.

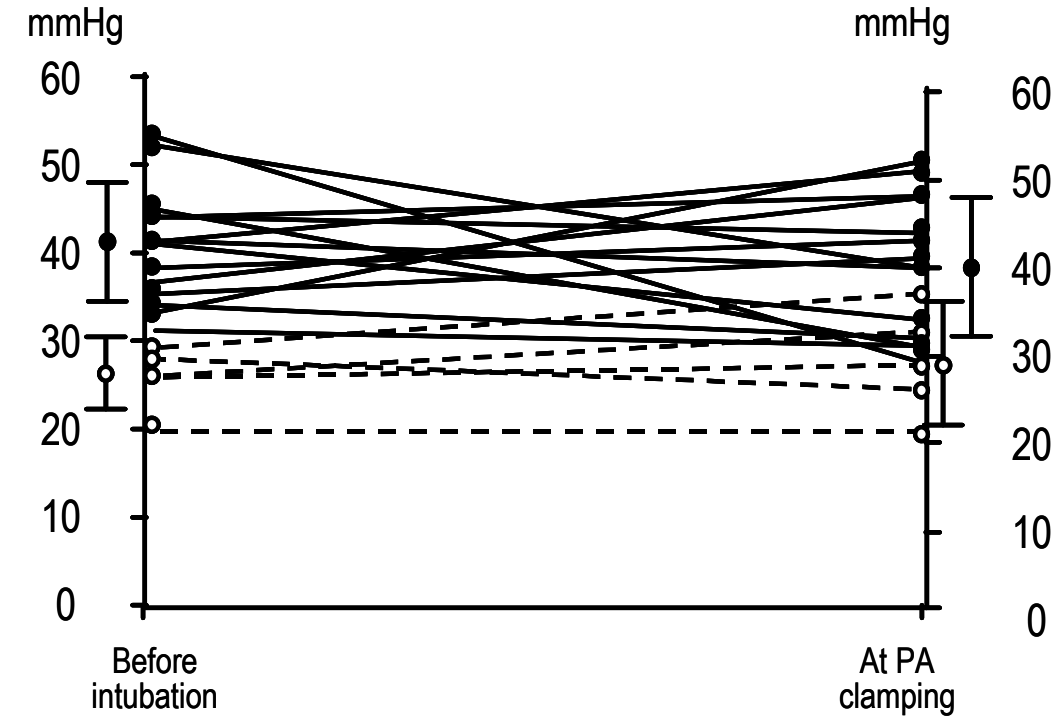


Figure 1.7.1.1. Changes in systolic PAP from awake to after clamping of the PA during pneumonectomy. Solid lines and circles indicate those subjects who had pulmonary hypertension, while dashed lines and open circles indicate those with normal PA, before PA clamping. The error bars indicate mean and one standard deviation of the two groups. No differences in PAP occurred from before to after PA clamping in either the group as a whole or in the subset of patients with pre-existing pulmonary hypertension. Lewis, Bastanfar et al, 1994

- Aalto-Setala and colleagues (Aalto, Heinonen et al. 1975) studied 11 patients with mild COPD undergoing surgery for pulmonary malignancy. No change in pulmonary artery pressure was found between two and one lung anesthesia, or with the application of $PEEP_5$ to the dependent lung.

- In a study in chronically instrumented dogs, Morgan and Guntheroth (Morgan and Guntheroth 1970) demonstrated that one lung anesthesia in the supine position induced a sixteen percent rise in PVR in the atelectatic lung. Such a rise in PVR in the atelectatic lung is expected, but the 8% rise in PVR in the ventilated lung was explained as being secondary to a decrease in lung volume. Mean PAP increased significantly albeit that the rise averaged only three mm Hg (Morgan and Guntheroth 1970).

- Pagel et al, (Pagel, Fu et al. 1998) have demonstrated that during one lung anesthesia with isoflurane, PAP, PVR and CVP rose. This did not happen with desflurane anesthesia. Mean PAP was 19 ± 5 mmHg at baseline and 25 ± 6 mm Hg while anesthetised before one lung ventilation commenced. Mean PAP rose to 27 ± 6 mmHg after initiation of OLA. This rise is unlikely to be of clinical significance.

It differentiates RV-PA interaction at PA clamping and at OLA.	Pulmonary artery pressure			Pulmonary vascular resistance	
	No change detected	Increase detected if no pre-existing PHPT	Increase detected if PHPT pre-exists	No change	Increase
ZEEP	Satoh, Sato et al. 1998; Fujita, Yamasaki et al. 1993; Cohen, Eisenkraft et al. 1988; Rogers and Benumof 1985; Aalto, Heinonen et al. 1975; Benumof and Wahrenbrock 1975	Werner, Malmkvist et al. 1984b; Malmkvist, Fletcher et al. 1989; Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Carlsson, Bindslev et al. 1985; Werner, Malmkvist et al. 1984; Pagel, Fu et al. 1998; Morgan and Guntheroth 1970	Lewis-JW, Bastanfar et al. 1994	Lewis-JW, Bastanfar et al. 1994 in 70% of patients; Carlsson, Bindslev et al. 1987 and Carlsson, Hedenstierna et al. 1987 and Carlsson, Bindslev et al. 1985 found no change in dependent lung PVR; Fujita, Yamasaki et al. 1993; Cohen, Eisenkraft et al. 1988;	Lewis-JW, Bastanfar et al. 1994 in 30% of patients; Morgan and Guntheroth 1970; Pagel, Fu et al. 1998
$PEEP_5$	Fujita, Yamasaki et al. 1993; Aalto, Heinonen et al. 1975			Fujita, Yamasaki et al. 1993; Inomata, Nishikawa et al. 1997	
$PEEP_{\geq 10}$	Cohen, Eisenkraft et al. 1988	Fujita, Yamasaki et al. 1993		Fujita, Yamasaki et al. 1993; Cohen, Eisenkraft et al. 1988	Inomata, Nishikawa et al. 1997
$CPAP_{10}$	Cohen, Eisenkraft et al. 1988				
$CPAP_{10}$ / $PEEP_{10}$	Cohen, Eisenkraft et al. 1988				

Table 1.7.1.1.1 The effects of one lung anesthesia on pulmonary artery pressures and pulmonary vascular resistance

- Lewis et al, (Lewis-JW, Bastanfar et al. 1994) investigated twenty patients with moderately severe chronic obstructive pulmonary disease undergoing pneumonectomy (Figure 1.7.1.1). They studied the interaction between the RV and the pulmonary vasculature on clamping the PA. They utilised a fast response thermodilution catheter capable of measuring RV ejection fractions and RV end-diastolic volumes. They reported the following results:
  - i. Preoperatively, 76.5% of these patients had **pulmonary hypertension**. 54% of this group demonstrated either a mean decrease of 8 mm Hg or no change in systolic and mean pulmonary artery pressure on clamping of the pulmonary artery. The other subjects in this group exhibited a mean 12 mm Hg rise in pulmonary artery systolic or diastolic pressures on PA clamping. However, when compared to the preoperative period, systolic (41 ± 7 vs. 41 ± 7 mm Hg) and mean (28 ± 5 vs. 30 ± 6 mm Hg) PA pressures did not differ on PA clamping.
  - ii. On the other hand, patients with **normal pulmonary artery pressures** exhibited only a 4 mm Hg

rise in mean PAP on clamping of the pulmonary artery (Figure 1.7.1.1).

iii. 94% of Lewis et al's (Lewis-JW, Bastanfar et al. 1994) patients had normal pulmonary vascular resistance preoperatively. Lewis and Bastanafar state that 30% of these patients demonstrated a rise in PVR on PA clamping to greater than 200 dynes.sec.cm^{-5}. However, the rise is clinically and statistically insignificant. The lack of difference also exists if data for the patients with pulmonary hypertension alone is analysed. Furthermore, PA clamping did not appear to increase opposition to RV ejection.

iv. Although this article does not study only the period of OLA, it is noteworthy for the following reasons;

i. It is one of only a few articles to studying RV coupling to its load using a fast response thermistor that involves pulmonary surgery,

ii. Data on RVEF during OLA are also tabulated in this study, albeit they are not commented on in the results or the discussion. They indicate that both opposition to pulmonary flow and RV performance did not change during OLA and,

iii. It emphasizes that the situation during OLA with and without PA clamping not always be comparable.

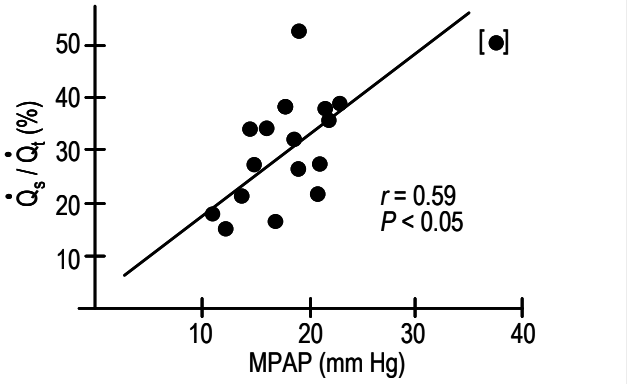


Figure 1.7.1.2. The relationship between pulmonary artery pressure and shunt is illustrated. Note that the data point in brackets represents a patient with partial obstruction of the lumen of the endobronchial tube. Redrawn from Malmkvist, Fletcher et al, 1989

In summary, the studies reported in humans or animals subject to OLA suggest that:

1. During OLA, in animals and humans with normal lungs and when IPPV is performed at zero end expiratory pressure, PVR does not change. Furthermore, pulmonary artery pressure does appear to increase, but by a clinically insignificant amount (Pagel, Fu et al. 1998; Inomata, Nishikawa et al. 1997; Wilson, Kapelanski et al. 1997; Chen, Lee et al. 1996; Cohen and Eisenkraft 1996; Fujita, Yamasaki et al. 1993; Fujita, Yamasaki et al. 1993; Cohen, Eisenkraft et al. 1988; Rogers and Benumof 1985; Aalto, Heinonen et al. 1975; Benumof and Wahrenbrock 1975).
2. If pulmonary hypertension pre-exists and one lung anesthesia is initiated, Lewis and colleagues suggest that indices of right ventricular afterload increase on PA ligation (Lewis-JW, Bastanfar et al. 1994). However, inspection of the data in the article reveals unconvincing evidence of these increases.

3. Some studies have however demonstrated clinically significant increases in mean PAP after initiation of one lung ventilation both at ZEEP, and with the application of PEEP or PEEP/CPAP (Pagel, Fu et al. 1998; Boldt, Papsdorf et al. 1997; Boldt, Muller et al. 1996; Malmkvist, Fletcher et al. 1989; Werner, Malmkvist et al. 1984; Werner, Malmkvist et al. 1984). Inomata suggested that the increase in PVR seen on application of 14 cm H_2O PEEP was an indication that the lung volume exceeded FRC.

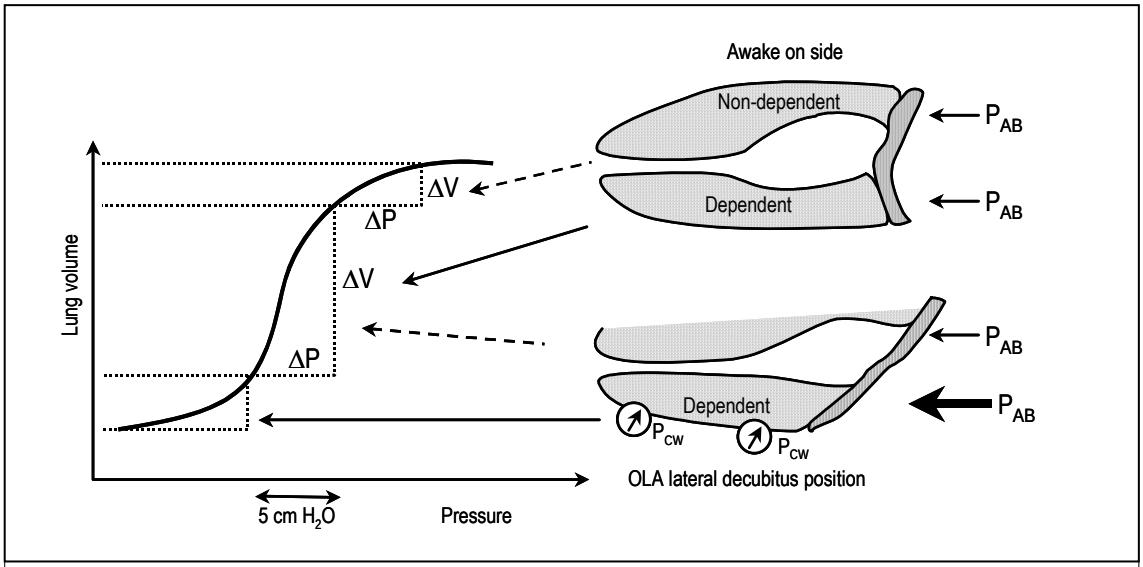


Figure 1.7.1.3. The decrease in FRC of the dependent lung in the lateral decubitus position: cause and effect. The effects of sub-optimal positioning with chest wall (P_{CW}) splinting, the weight of the mediastinum and abdominal contents (P_{AB}) on the paralyzed diaphragm is illustrated in decreasing lung volume of the dependent lung. The effect of this on the position of the dependent lung and on the pressure volume relationship of the lung is illustrated. Adapted from Cohen, 1995 and Benumof, 1991

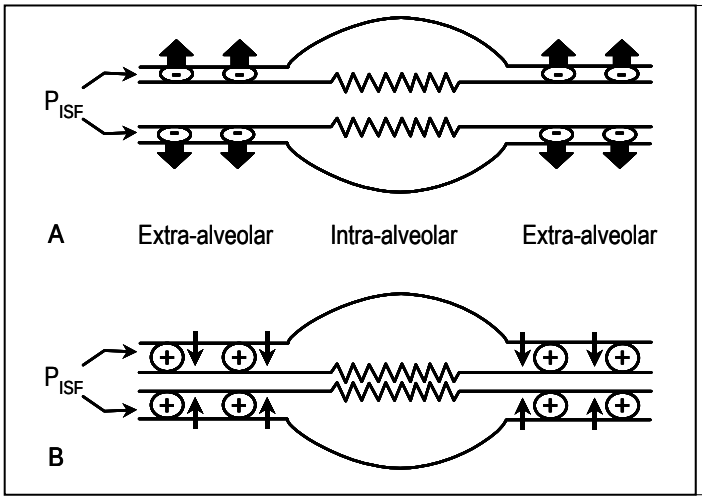


Figure 1.7.1.4. The Effect of pulmonary interstitial pressure on extra-alveolar vessels: The creation of zone 4 conditions.

A: in normal lungs, the negative interstitial pressure (P_{ISF}) maintains patency of the extra-alveolar vessels.

B: If P_{ISF} exceeds venous and alveolar pressures, the extra-alveolar vessels will be less expanded and their resistance will increase. This creates zone 4 conditions.

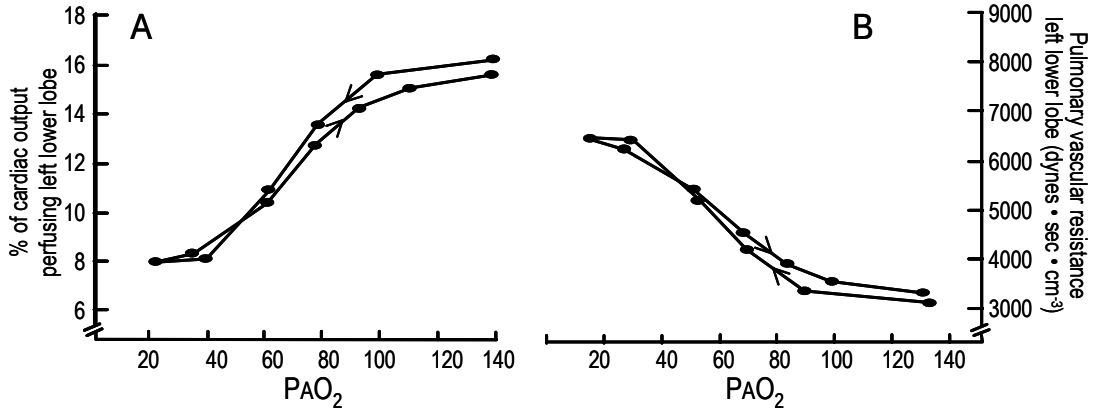


Figure 1.7.1.5. Benumof and Wahrenbrock selectively induced hypoxia in the left lower lobe of open-chested dogs. This resulted in a 51% decrease in electromagnetically measured blood flow to the lobe and to an increase in the pulmonary vascular resistance of 132% of that lobe. P_AO_2 is measured in mm Hg. Redrawn from Benumof and Wahrenbrock, 1975

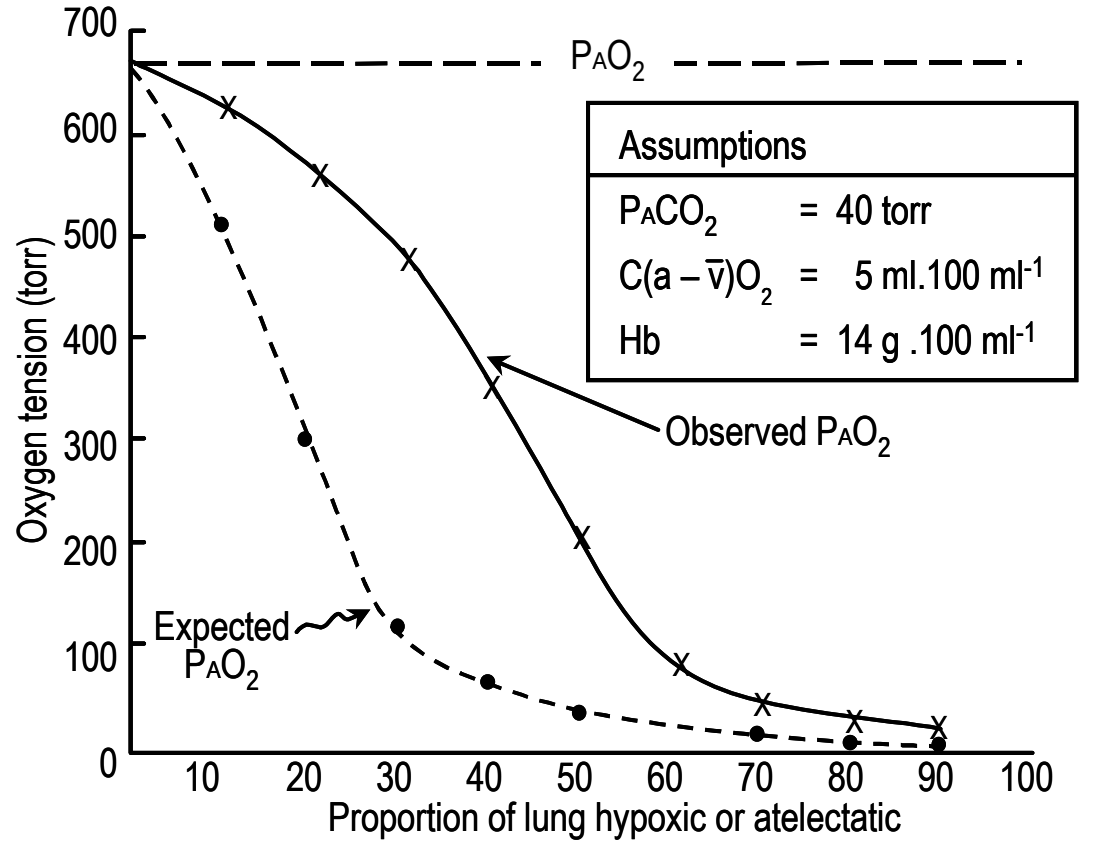


Figure 1.7.1.6. The predicted PaO_2 if different percentages of the lung are made hypoxic. With HPV, the PaO_2 is reflected by the solid line, and in the absence of HPV, by the dashed line. HPV is most effective when approximately half of the lung is hypoxic or atelectatic. Redrawn from Domino, 1997

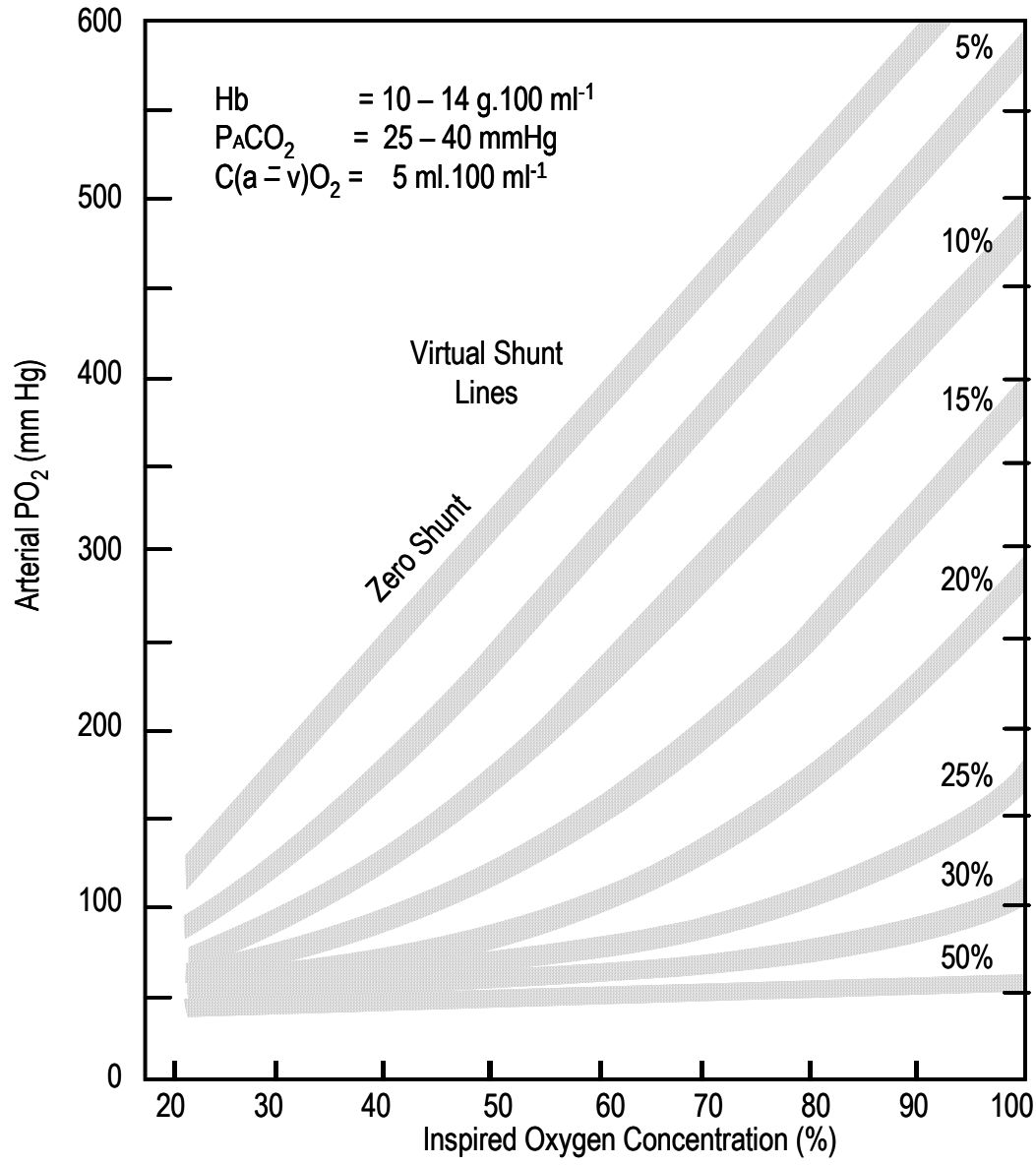


Figure 1.7.1.7. Isoshunt lines. A 40 to 50% shunt will result in severe hypoxemia even with the administration of 100% oxygen and with effective ventilation. However, the typical 20 to 35% shunt that is induced by HPV is addressable with 100% oxygen.

Redrawn from Nunn, 1987

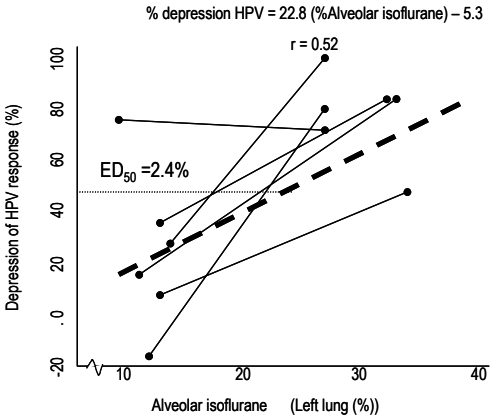


Figure 1.7.1.8 The influence of isoflurane dose on the HPV response in animals. For each dog, the maximal HPV response was identified as the difference between the shunt in the left lung during normoxia and the shunt during left lung hypoxia. The reduction of HPV response when isoflurane was administered was calculated as a percent of this maximum and is plotted on the ordinate of this figure. The left lung isoflurane concentration is represented in % on the abscissa. The linear regression and correlation is indicated. Redrawn from Domino, Borowec and colleagues, 1986

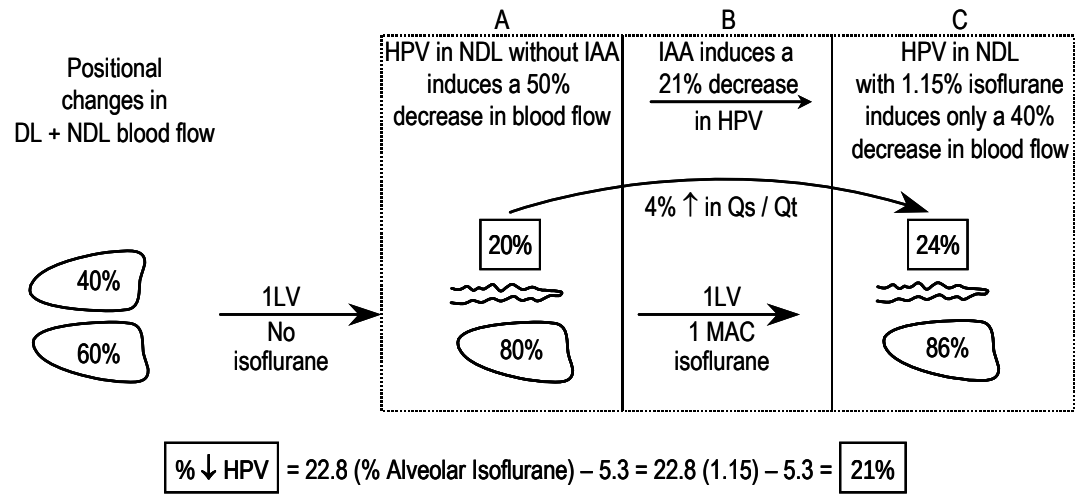


Figure 1.7.1.9. Diagrammatic representation of the effect of an alveolar concentration of 1 MAC isoflurane on blood flow distribution during one lung ventilation. See text for explanation. (1LV = one lung ventilation; HPV = hypoxic pulmonary vasoconstriction; MAC = minimum alveolar concentration; Qs/Qt = shunt fraction). Redrawn from Benumof, 1986

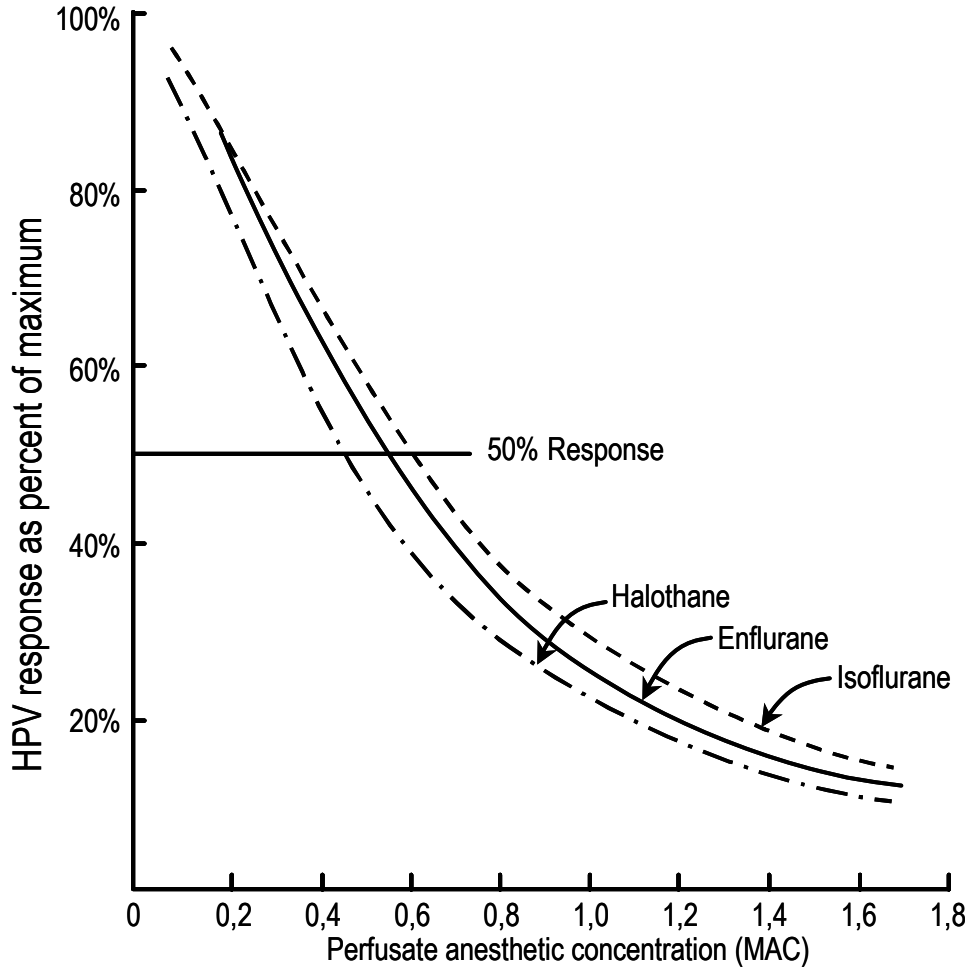


Figure 1.7.1.10. Dose response curves for inhibition of HPV by IAA's in vitro isolated rat lungs. Note that the curves for various anesthetic agents do not differ in slope, position or ED_{50}. ($r > 0.82$). Domino, 1997

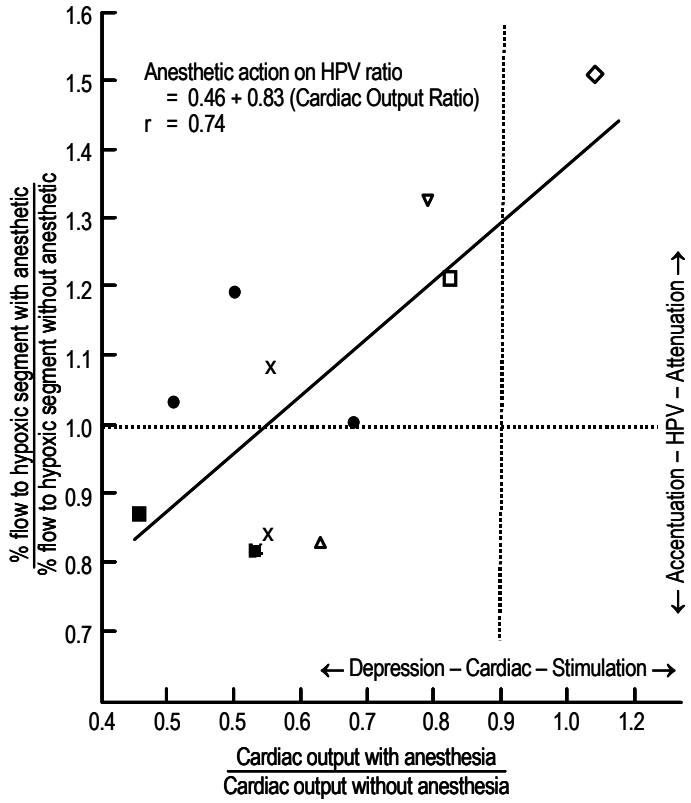


Figure 1.7.1.11. The effects of IAA's on the relationship between the observed changes in HPV with changes in cardiac output. The baseline cardiac output on the x-axis without the administration of IAA is designated as one. The effect of the IAA on HPV is indicated by the percentage flow to the atelectatic segment with IAA / Without IAA on the y-axis: A ratio of more than one indicates inhibition of HPV. There is a linear relationship between cardiac output and attenuation of HPV (c.f. Figure 1.7.1.2). The different shapes represent different IAA's: halothane, isoflurane, methoxyflurane, nitrous oxide, trichlorethylene, diethyl ether and enflurane. Redrawn from Domino, 1997

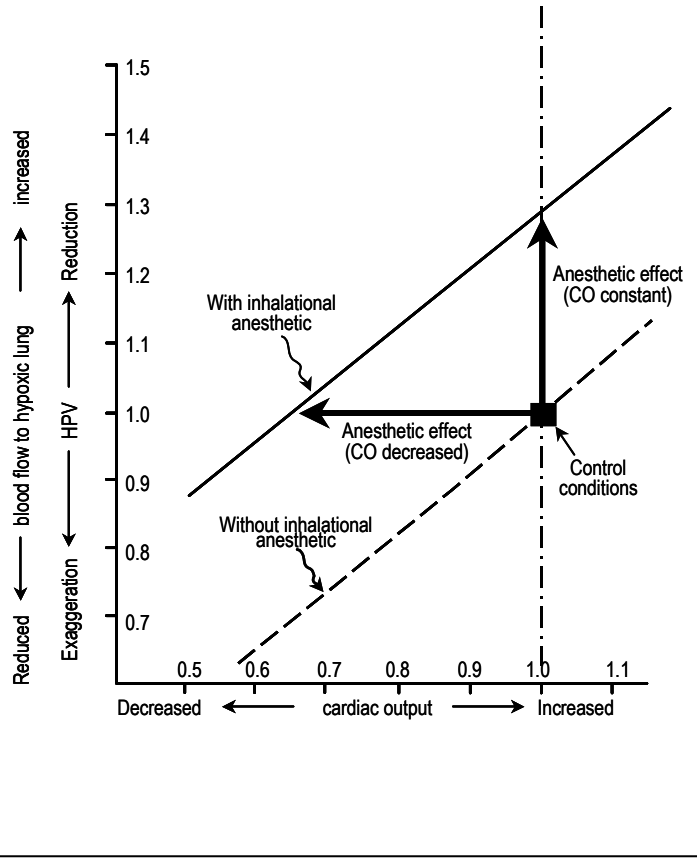


Figure 1.7.1.12. A diagram of the effect of IAA on the observed response to HPV. Relative cardiac output (x axis) is plotted against the apparent HPV effect as in diagram 1.7.1.11. The dashed line represents the change in blood flow to the hypoxic lung as predicted by changes in cardiac output. The solid line parallel to it represents the same relationship, but in the presence of IAA's. The vertical arrow indicates the true reduction of HPV by IAA when the cardiac output does not change. The horizontal arrow represents the apparent effect when a decrease in cardiac output leads to a decrease in PvO_2, which on the one hand, potentiates HPV. On the other hand, the IAA contributes to direct depression of HPV. When these two effects act in combination, the result is an unchanged blood flow to the hypoxic lung. Redrawn from Domino, 1997

1.7.1.2 Causes of an increase in PVR and PA pressure during one lung anesthesia

1.7.1.2.1 The decrease in lung volume of the dependent lung

Lung volume (at end expiration this is represented by the functional residual capacity) decreases:

- By 20 to 25% on assuming the supine position when awake (Wahba 1991) with
- A further decrease of approximately 20% on induction of anesthesia in the supine position (Rothen 1997; Wahba 1991; Nunn 1987). Greater decreases occur in obese patients (Wahba 1991).

Dependent lung volume may be decreased by pre-existing damage. This may occur secondary to similar processes as occurred in the lung being operated on. This is especially important in the Western Cape with the high incidence of pulmonary tuberculosis (Cohen 1995; Benumof 1991; Katz, Laverne et al. 1982). Causative factors include:

1. A decrease in chest wall compliance of the of the dependent lung due to the weight of the chest (splinting);
2. The weight of the mediastinum and the non-dependent lung;
3. Surgical manipulation of the non-dependent lung;
4. The abdominal contents exert greater pressure on the diaphragm of the dependent lung which aggravates the decrease in functional residual capacity;
5. Use of 100% oxygen leads to absorption atelectasis;
6. The development of atelectasis may be aggravated by airway obstruction from secretions, blood or pus from the non-dependent lung, poor muco-ciliary clearance during anesthesia and an incorrectly placed double lumen endotracheal tube (DLT).
7. Zone 4 conditions may occur at the bottom of the non-dependent lung. This zone is created either when a very low lung volume exists or transudation of fluid into the interstitial compartment occurs. These situations produce a positive interstitial pressure that results in an increase in extra-alveolar vessel compression and resistance with subsequent decrease in pulmonary blood flow to this zone (Figure 1.7.1.4); i.e. in zone 4 conditions, pulmonary arterial pressure > *interstitial pressure* > pulmonary venous pressure > alveolar pressure. The patency of the extra-alveolar vessels, and therefore the blood flow through this area, is governed by the difference between pulmonary arterial and interstitial pressure.

The decrease in lung volume leads to an increase in pulmonary vascular resistance because of the decrease in size of the extra-alveolar vessels. This may impact adversely on right ventricular function (Lewis-JW, Bastanfar et al. 1994). Furthermore, the decrease in lung volume leads to the dependent lung being in a worse position on the pressure-volume relationship with a decrease in its compliance (Figure 1.7.1.3) (Cohen 1995). This decrease in compliance may result in higher airway pressures during one lung anesthesia with adverse effects on right ventricular pre– and afterload (Aalto, Heinonen et al. 1975).

1.7.1.2.2 Hypoxic pulmonary vasoconstriction

Barer and colleagues were some of the first people to study the effects of alveolar hypoxia on pulmonary blood flow. They elegantly described hypoxic pulmonary vasoconstriction (HPV) in the following words: *"The effects of bronchial occlusion on the pulmonary circulation were studied. … Blood flow fell rapidly at normal PAP, … and in constant flow experiments, PAP rose. We conclude that an active … increase in vasomotor tone was involved"* (Barer, Howard et al. 1969).

Hypoxic pulmonary vasoconstriction is the principal mechanism whereby the resistance of hypoxic areas of the lung increases and blood flow is redirected. This results in limitation of the shunt fraction (Figure 1.7.1.5) (Benumof 1991; Siegel and Brodsky 1991; Benumof 1985; Pirlo, Benumof et al. 1981; Bjertnaes, Mundal et al. 1980; Benumof 1979; Benumof and Wahrenbrock 1975). Without HPV, 40 to 50% of the cardiac output would flow through the non-dependent lung during OLA. As a result of HPV, only 20 to 40% of the cardiac output is shunted through the non-dependent lung (Benumof 1991; Rogers and Benumof 1985; Glasser, Domino et al. 1983; Fiser, Friday et al. 1982; Khanam and Branthwaite 1973; Tarhan and Lundborg 1970; Tarhan and Lundborg 1968). This represents a decrease in the shunt to more manageable proportions (manageable in terms of arterial oxygenation) during one lung anesthesia (Figures 1.7.1.6 and 1.7.1.7) (Glasser, Domino et al. 1983). HPV is therefore of importance in regulating the relative pulmonary vascular resistances, the distribution of flow between the dependent and non-dependent lungs, and the shunt which plays a pivotal role in arterial oxygenation during one lung anesthesia.

Factors relevant to this study that affect HPV during one lung anesthesia will be examined. The relative magnitude of the collapse and tortuosity of the pulmonary vessels compared to the effects of HPV in decreasing flow to an atelectatic area has been quantified (Benumof 1991; Benumof 1985). Whereas two studies from the same laboratory conducted in dogs report that limitation of flow is entirely due to hypoxic pulmonary vasoconstriction (Figure 1.7.1.5) (Pirlo, Benumof et al. 1981; Bjertnaes, Mundal et al. 1980; Benumof 1979), other work has demonstrated that mechanical obstruction accounts for approximately 6% of the rise in PVR during atelectasis (Bjertnaes, Mundal et al. 1980). Furthermore, it appears that P□O_2 also plays an important role in the initiation of HPV (Siegel and Brodsky 1991). A deviation from normal P□O_2 affects hypoxic pulmonary vasoconstriction due to diffusion of oxygen to or from the intravascular space. An increase in the P□O_2 inhibits HPV in hypoxic areas of the lung, and a decrease therein promotes HPV in otherwise normoxic areas of the lung (Pease, Benumof et al. 1982; Benumof, Pirlo et al. 1981).

Intravenous anesthetic agents, including opioids, do not appear to have measurable effects on hypoxic pulmonary vasoconstriction, pulmonary vascular resistance and arterial oxygenation (Domino 1997; Reid, Slinger et al. 1996; Chen and Marshall 1995; Siegel and Brodsky 1991; Steegers and Backx 1990; Benumof, Augustine et al. 1987; Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Rogers and Benumof 1985; Rees and Gaines 1984). However, the inhalation anesthetic agents have been demonstrated to inhibit HPV in a dose dependent manner secondary to their effects on smooth muscle (Figures 1.7.1.8, 1.7.1.9 and 1.7.1.12) (Pagel, Fu et al. 1998; Domino 1997; Groh, Kuhnle et al. 1995; Mathers, Benumof et al. 1977). Domino and her colleagues (Domino, Borowec et al. 1986) have quantified the dose dependent inhibitory effects of isoflurane on hypoxic pulmonary vasoconstriction in dogs independent of its effects on cardiac output or P□O_2 (Figure 1.7.1.8 and 1.7.1.9). The

relationship between percentage inhibition by isoflurane on HPV was calculated as: 22.8 x % alveolar isoflurane 5.3♣ (Domino, Borowec et al. 1986). Thus, a 0.5 x and a 1 x MAC end tidal partial pressure of isoflurane would inhibit hypoxic pulmonary vasoconstriction by 10.5% and 21% respectively. This would consequently increase shunt from 20%, to 22% and 24%, and decrease PaO_2 from 37.3 kPa to 27.3 kPa while administering 100% oxygen (Figures 1.7.1.7 and 1.7.1.9) (Benumof 1991; Benumof, Augustine et al. 1987; Bergel and Milnor 1965).

The depressant effects of the inhalation agents on the circulation might counteract their direct inhibition of HPV (Benumof 1986; Domino, Borowec et al. 1986; Rees and Gaines 1984). If the IAA's decrease cardiac output, the resultant decrease in P□O_2 will potentiate HPV and thereby decrease shunt (Domino 1997; Siegel and Brodsky 1991; Benumof 1986; Mathers, Benumof et al. 1977) (Figures 1.7.1.11 and 1.7.1.12). This decrease in P□O_2 coupled with a *decrease* in pulmonary artery pressure are suggested to be major reasons why inhalation agents produce minimal effects on PaO_2 and shunt fraction and are well tolerated during one lung anesthesia despite directly inhibiting HPV (Figure 1.7.1.9) (Domino 1997; Siegel and Brodsky 1991; Benumof, Augustine et al. 1987; Carlsson, Bindslev et al. 1987; Benumof 1986; Domino, Borowec et al. 1986; Benumof and Wahrenbrock 1975). What is of concern however is that a change in P□O_2 will affect the PVR of both lungs. A decrease in P□O_2 will cause an increase in the PVR in the ventilated, dependent lung. This will act to redirect blood to the non-dependent lung and result in an increase shunt fraction (Siegel and Brodsky 1991).

Factors other than anesthetic drugs may have an influence on HPV during one lung anesthesia (Benumof 1986):

- Shunt fraction has shown to be higher in surgical patients due to local inhibition of HPV by the manipulation of the lung (Benumof 1991; Siegel and Brodsky 1991; Benumof 1986). Surgical stimulation may be cause the release of vasodilators such as prostaglandins (Boldt, Papsdorf et al. 1997; Scherer, Van Aken et al. 1984). This may contribute to an increase in shunt fraction.
- Hyper– and hypocapnia have direct (via their effects on pH) and indirect effects on HPV (Benumof 1991). Hypercapnia promotes HPV. However, hypercapnia will concomitantly increase PVR of the ventilated dependent lung, which will promote shunting of blood via the non-dependent lung. The indirect effects of hypercapnia are related to the concomitant hypoventilation of the dependent lung, with a decrease in lung volume, development of low V/Q units and an increase in PVR (Benumof 1991). Hypocapnia on the one

♣ In the study conducted by Domino and her colleagues (Domino, Borowec et al. 1986), the alveolar isoflurane concentration was calculated using a modification of the alveolar gas equation:

$$FA_{ISO} = [FI_{ISO}] - [[(FA_{CO2} - FI_{CO2})]/(FE_{CO2} - FI_{CO2})] \times [FI_{ISO} - FE_{ISO}]]$$

Where

- FI_{ISO} is the mixed inspired isoflurane concentration expressed as fractional concentration of the inspired mixture,
- FE_{ISO} is the mixed expired isoflurane concentration expressed as fractional concentration of the expired mixture,
- FA_{CO2} is the alveolar carbon dioxide concentration. This is estimated from the arterial carbon dioxide partial pressure,
- FI_{CO2} is the inspired carbon dioxide concentration and,
- FE_{CO2} is the mixed expired carbon dioxide concentration.

hand, inhibits hypoxic pulmonary vasoconstriction (Benumof, Mathers et al. 1976; Benumof and Wahrenbrock 1975). On the other hand, the increase in tidal volume and respiratory rate required to induce hypocapnia may cause an increase in lung volume and pulmonary vascular resistance resulting in diversion of blood flow away from the dependent lung and to wards the non-dependent lung. This shift may aggravate the shunt fraction during OLA.

- The presence of pre-existing disease in the dependent lung limits the ability of its vascular bed to undergo recruitment and dilation and accept the increase in the percentage of the cardiac output that is distributed to it during one lung anesthesia (Benumof 1986). This may increase the shunt flow directed via the non-dependent lung (Benumof 1986; Scanlon, Benumof et al. 1978).
- Furthermore, pre-existing disease in the non-dependent lung may limit the ability of the lung to initiate hypoxic pulmonary vasoconstriction (Benumof 1991; Benumof 1986; Zapol and Snider 1977). However pre-existing disease in the non-dependent lung may significantly limit flow to that side with favourable effects on shunt during one lung anesthesia (Benumof 1986).(Benumof 1991; Benumof 1985)
- Both high and low pulmonary artery pressures affect hypoxic pulmonary vasoconstriction. High pulmonary artery pressures compete with the smooth muscle in the vessel walls: as the normal pulmonary arteries have poor musculature, high pulmonary artery pressure will force the vasoconstricted channels open. Low pulmonary artery pressure would enable zone one conditions in the “upper” part of the lung resulting in an increase in resistance (Benumof 1991; Scanlon, Benumof et al. 1978; Colley, Cheney et al. 1977; Benumof and Wahrenbrock 1975).
- When the percentage of the lung that is hypoxic is between 30 to 70% (typically the amount of lung that is hypoxic during one lung anesthesia), HPV is maximal and will positively influence PaO_2 (Figure 1.7.1.6) (Benumof 1991). When greater amounts of the lung are hypoxic, the ability to redistribute more blood away from the hypoxic area becomes proportionally less (Scanlon, Benumof et al. 1978).

1.7.1.2.3 An increase in lung volume

Should the volume of the dependent lung exceed functional residual capacity, compression of alveolar capillaries and stretching of the extra-alveolar vessels with an increase in pulmonary vascular resistance will result (West 1985). Furthermore, compromise of venous return due to the increase in intrathoracic pressure and direct compression of the heart, a situation analogous to tension pneumothorax, may occur (Conacher 1998; Myles, Weeks et al. 1997). Causes of an increase in lung volume of the dependent lung during one lung anesthesia include:

1. Excessive intrinsic or extrinsic PEEP. Even modern plastic double lumen tubes with better inner diameter to wall thickness ratios than their older rubber counterparts have been shown to result in significant amount of intrinsic PEEP (Inomata, Nishikawa et al. 1997). This may be compounded by lung units with slow time constants (i.e. high airway resistance due to secretions (Conacher 1998; Myles, Weeks et al. 1997; Raffin, Michel-Cherqui et al. 1992), bronchospasm, low lung volumes, kinked, poorly positioned or inappropriately small double lumen tubes and high pulmonary compliance in patients with COPD). If this is additionally combined with a relatively short time in which expiration is allowed to occur (high respiratory rate as usually recommended during one lung ventilation), dynamic hyperinflation may ensue (Conacher 1998; Inomata, Nishikawa et al. 1997; Slinger, Hickey et al. 1989).
2. Excessive tidal volumes, especially when combined with factors that aggravate dynamic hyperinflation and intrinsic PEEP (Ranieri, Mascia et al. 1995).

3. A pneumothorax, or bullus on the ipsilateral side as the dependent lung that has greatly distended during one lung ventilation, will produce similar effects as those described above.

Excessive CPAP to the non-dependent lung, in the presence of an open chest that does not limit lung distension, may increase pulmonary vascular resistance of that lung.

1.7.2 The performance of the right ventricle during one lung anesthesia

1.7.2.1 Studies emphasizing right ventricular function during one lung anesthesia

Only very few studies (Fujita, Yamasaki et al. 1993) have specifically studied the function of the right ventricle during one lung anesthesia:

- Fujita and colleagues (Fujita, Yamasaki et al. 1993) used sonomicrometers to study the effect of sevoflurane on right ventricular function during one lung anesthesia in healthy sheep. The aims of their study were *"to examine the effect of sevoflurane on right ventricular function, the safety of sevoflurane for one lung ventilation and the effects of PEEP to the dependent lung".* They found no difference on the

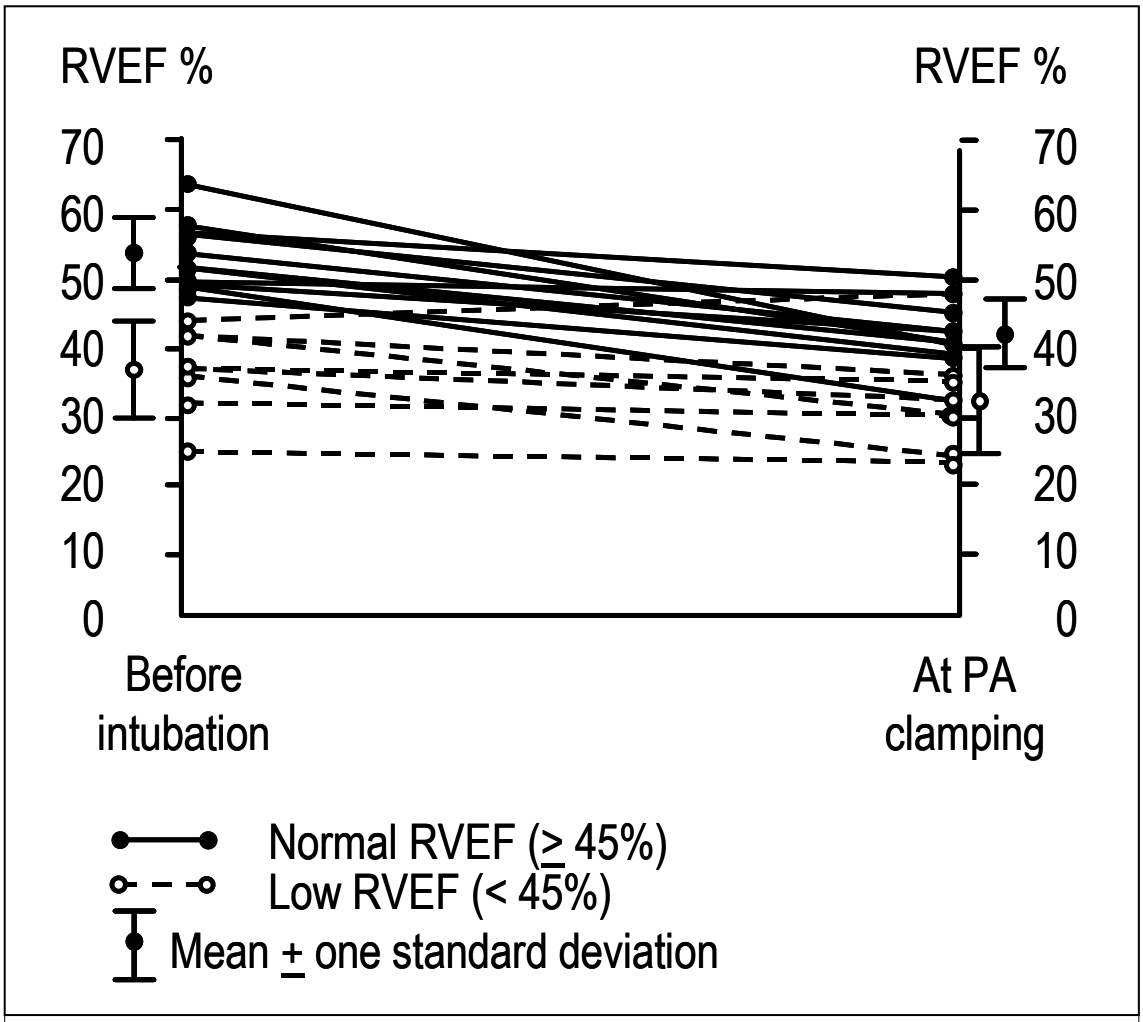


Figure 1.7.2.1. The changes in RVEF during pneumonectomy. Lewis, Bastanfar et al, 1994

shortening fraction in these two areas when comparing ZEEP, $PEEP_5$, and $PEEP_{10}$. They did not report on Ea or Ees data.

Other studies (Inomata, Nishikawa et al. 1997; Lewis-JW, Bastanfar et al. 1994) have studied global hemodynamics and/or right ventricular function after PA clamping and/or lung resection:

- Inomata and colleagues (Inomata, Nishikawa et al. 1997) *investigated the level of PEEP that would optimise both hemodynamics and oxygenation* during one lung anesthesia. They studied eight patients without COPD scheduled for lobectomy. The anesthetic regimen comprised fentanyl, isoflurane and nitrous oxide. Up to 7.8 cm H_2O PEEP applied to the dependent lung resulted in an increase in RVEF from 30 ± 11% to 38 ± 8%, but PVR was unchanged when compared to ZEEP. On applying a further 6.5 cm H_2O PEEP to the dependent lung, a decrease in RVEF to 33 ± 9% and cardiac index (from 3.14 ± 0.74 to 2.75 ± 0.86 litres.$min^{-1}.m^{-2}$) was detected (Inomata, Nishikawa et al. 1997). Inomata et al, suggest that at these levels of PEEP, alveolar capillary compression was induced as reflected by the increase in pulmonary vascular resistance (Figures 1.7.3.1 and 1.7.3.2) (Inomata, Nishikawa et al. 1997).

- Boldt and colleagues (Boldt, Muller et al. 1996) designed a study to investigate *"cardiopulmonary alterations in patients undergoing pulmonary resection under standardized conditions, whether the kind of anesthetic management technique affects hemodynamics, and whether early or late extubation has any negative consequences"*. Hemodynamics were recorded after induction of anesthesia, before initiation of surgery, 30 minutes after initiating one lung anesthesia, at the end of surgery and postoperatively. Pneumonectomy, but not *lobectomy*, was associated with a deterioration in right ventricular function (a decrease in RVEF from 40.6 ± 3.4%) to 28.8 ± 4.3%, and increases in RVEDVI (85 ± 16) to 116 ± 21 $ml.m^{-2}$, CVP (10 ± 3.6 to 14.8 ± 3.1 mm Hg) and PAWP (12.2 ± 2.9 to 18.3 ± 3.8 mm Hg). Boldt and his colleagues comment on their findings as follows: "*an increase in right ventricular afterload associated initially with one lung anesthesia and subsequent pneumonectomy may lead to an increase in right ventricular end-diastolic volume, a decrease in EF with septal shift and reduced left ventricular filling but increased LVEDP*".

- Lewis et al, (Lewis-JW, Bastanfar et al. 1994) also studied patients who had mild COPD undergoing pneumonectomy. Their aims were to determine predictors of late cardiopulmonary function. RVEF was normal (> 45%) preoperatively in 59% of the patients. On clamping of the pulmonary artery, two types of response were observed: 70% of the patients demonstrated a decrease in RVEF to less than 45%, and in 25% of patients, RVEF fell below 35%. RVEF was closely related to right ventricular stroke work index and inversely to right ventricular end-diastolic volume index (Figure 1.7.2.1). There were no changes in RVEDVI, central venous pressure or PAWP and no correlation between pulmonary vascular resistance, pulmonary artery pressure and RVEF.

- The intraoperative decrease in EF and increase in RVEDV has been shown to continue postoperatively (Okada, Ishii et al. 1996; Okada, Ota et al. 1994; Lewis-JW, Bastanfar et al. 1994; Reed, Spinale et al. 1992). In the study by Lewis et al, (Lewis-JW, Bastanfar et al. 1994), a RVEF of less than 35% on pulmonary artery clamping accurately identified patients in whom limitation of exercise capacity (NYHA

class 3 or 4) was evident 9.7 ± 6.3 months after surgery. It is interesting to note that a preoperative PVR/RVEF ratio greater than five predicted long-term exercise limitation (a NYHA classification of 3 or 4) in 5 out of 6 patients undergoing pneumonectomy (Lewis-JW, Bastanfar et al. 1994). No other preoperative tests predicted this deterioration in postoperative cardiopulmonary status (Lewis-JW, Bastanfar et al. 1994). Amar and colleagues also studied perioperative RV function in patients undergoing both lobectomy and pneumonectomy. The tool that these investigators used was echocardiography (Amar, Burt et al. 1996). They found that pneumonectomy, but not lobectomy, was associated with a postoperative increase in systolic pulmonary artery pressure (31 ± 15 versus 25 ± 10 mmHg respectively). Nonetheless, this moderate degree of increase in pulmonary artery pressure was not associated with any evidence of RV dysfunction. However, two of the three patients who developed acute respiratory distress syndrome postoperatively also developed RV dilation. These two patients with two-organ dysfunction died postoperatively (Amar, Burt et al. 1996).

- Okada et al, (Okada, Ota et al. 1994) suggested that the RV adapts to increases in afterload by dilation, which may only be evident on exercise. They subsequently investigated this hypothesis in candidates scheduled for lung resection by studying the preoperative predictive value of RVEF during exercise (Okada, Ishii et al. 1996). A decrease in RVEF on exercise predicted a decrease in postoperative RVEF, and was found to be a better predictor of complications (e.g. arrhythmias, pneumonia) than the absolute value of this parameter.

- The increase in RVEDV and decrease in RVEF have been related to the development of atrial fibrillation after lung resection (Backlund, Laasonen et al. 1998; Okada, Ota et al. 1994). A study by Backlund and colleagues was not able to demonstrate a relationship between the above, albeit that immediate postoperative right ventricular pressure, greater volumes of intraoperative fluid and preoperative increased PVR *was* associated with the subsequent development of atrial fibrillation (Backlund, Laasonen et al. 1998).

Thus, in summary, right ventricular dysfunction during one lung anesthesia appears to occur:

1. At too small or large lung volumes, but is not often associated with a measured increase in PVR,
2. During pneumonectomy rather than lobectomy,
3. Is predicted by a preoperative decrease in RVEF on exercise and by a PVR/RVEF ratio > 5,
4. It is noteworthy that the deterioration in right ventricular function is not always associated with a measurable increase in total pulmonary vascular resistance or pulmonary artery pressure (Backlund, Laasonen et al. 1998; Freden, Wei et al. 1995) and,
5. Dysfunction may continue for months postoperatively and be responsible for the subsequent limitation of exercise capacity

1.7.2.2 One lung anesthesia, systemic hemodynamics and oxygen delivery

Few studies have specifically addressed the effect of initiating one lung ventilation on hemodynamics and oxygen flux: most of the studies discussed below have addressed the effects of various manoeuvres on shunt and have

serendipitously included hemodynamic values in their tables of data.

Many studies have reported that no change in cardiac output occurs during one lung ventilation (Wilson, Kapelanski et al. 1997; Boldt, Muller et al. 1996; Chen, Lee et al. 1996; Malmkvist, Fletcher et al. 1989; Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Jenkins, Cameron et al. 1987; Carlsson, Bindslev et al. 1985; Rogers and Benumof 1985; Katz, Laverne et al. 1982; Rees and Wansbrough 1982a; Bachand, Audet et al. 1975; Morgan and Guntheroth 1970; Morgan and Guntheroth 1970; Morgan and Guntheroth 1970). However there are a number of studies that have demonstrated an increase in cardiac output, VO_2 and DO_2 and a decrease in SVR on initiation of one lung anesthesia (Zaune, Knarr et al. 1990).(Pagel, Fu et al. 1998; Cohen, Eisenkraft et al. 1988; Thys, Cohen et al. 1988; Aalto-Setala and Heinonen 1982; Aalto, Heinonen et al. 1975):

- Aalto-Setala and colleagues (Aalto-Setala, Heinonen et al. 1975) compared hemodynamics during one and two-lung ventilation. They described a greater than 10% decrease in two, and an increase in another two of the 11 patients studied, of both cardiac output and oxygen delivery. In a subsequent study, the same group described a small increase in stroke volume, cardiac output and oxygen delivery on initiation of one lung anesthesia (Aalto-Setala and Heinonen 1982). What is also interesting that they described an inverse relationship between cardiac index and plateau airway pressure during one lung ventilation (Figure 1.7.2.2).
- On initiation of one lung anesthesia, Cohen and co-workers (Cohen, Eisenkraft et al. 1988) described an increase in cardiac output from 3.57 ± 0.17 to 4.5 ± 0.26 $l.min^{-1}$. Anesthesia was maintained with isoflurane and 50% nitrous oxide and the authors suggest that the increase in cardiac output could be attributed to a "fairly light level of anesthesia" or an autonomic reflex on initiation of one lung anesthesia (Cohen, Eisenkraft et al. 1988).

Therefore, it appears that anesthetic agents used may have an influence on cardiac output and delivery of oxygen during one lung anesthesia (Boldt, Muller et al. 1996; Cohen, Eisenkraft et al. 1988; Rees and Wansbrough 1982a).

Variable effects of PEEP and CPAP on hemodynamics during one lung anesthesia have been described, but many

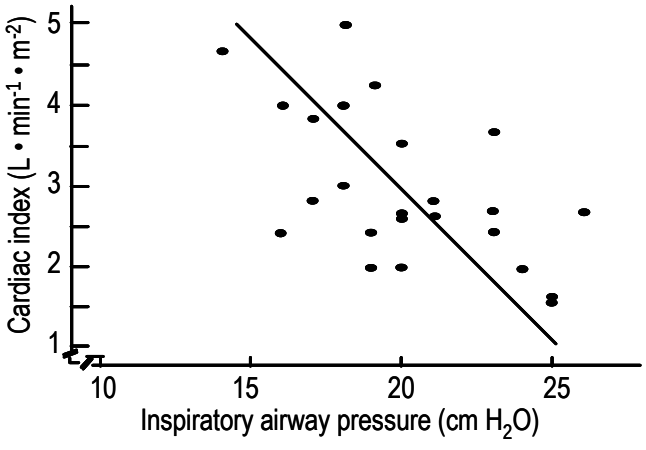


Figure 1.7.2.2. Relationship between plateau inspiratory airway pressure and cardiac index during one lung anesthesia. r = - 0.5894, p < 0.001. Redrawn from Aalto-Setala, Heinonen and colleagues, 1975

of the studies have reported a decrease in cardiac output:

- Cohen and co-workers (Cohen, Eisenkraft et al. 1988) found no changes in hemodynamics when $PEEP_{10}$ compared to ZEEP was applied to the dependent lung. However on application of $PEEP_{10}/CPAP_{10}$ to the dependent and non-dependent lungs respectively, cardiac output decreased.
- In a subsequent study, Cohen and colleagues (Cohen, Thys et al. 1985a) compared the effect of a combination of CPAP and PEEP to the dependent and non-dependent lungs respectively during right and left thoracotomy. They described a decrease in cardiac output (4.8 ± 1.3 to 3.79 ± 0.8 $l.min^{-1}$) only when $PEEP_{10}/CPAP_{10}$ was administered which they suggested was due to the "increase in positive pressure in both lungs". No other differences in hemodynamics were elicited by the manoeuvres applied to either lung during one lung anesthesia.
- Cohen and colleagues (Cohen, Thys et al. 1985b) also reported on the effects of applying $PEEP_{10}$ to the dependent lung during one lung anesthesia during isoflurane and 50% nitrous oxide anesthesia in humans. Cardiac output decreased significantly from 5 ± 1.1 to 3.9 l ± 1.0 $litres.min^{-1}$.
- Cohen et al, (Cohen and Eisenkraft 1996) have differentiated between the effects of $PEEP_{10}$ to the dependent lung in patients who are or are not hypoxic during one lung anesthesia. Administration of $PEEP_{10}$ elicited no difference on the cardiac output between these two groups. They suggest that dependent lung volume and PVR were favourably affected in the hypoxic group, but this had no effect on total cardiac output (Cohen and Eisenkraft 1996).
- Inomata et al, (Inomata, Nishikawa et al. 1997) demonstrated no change in cardiac index or delivery of oxygen during one lung anesthesia when ZEEP or an amount of PEEPe equal to the PEEPi present (up to 7.8 cm H_2O PEEP) was applied to the dependent lung. However when an additional 6.5 cm H_2O PEEP was applied to the dependent lung, both cardiac index and oxygen delivery decreased.
- Capan et al, (Capan, Turndorf et al. 1980) systematically studied the effects of PEEP and/or insufflation of oxygen to the non-dependent lung with or without positive airway pressure on arterial oxygenation during one lung anesthesia. Cardiac output was unchanged during application of CPAP or insufflation of oxygen to the non-dependent lung. However $PEEP_{10}$ to the dependent lung resulted in a 9% decrease in cardiac output (Capan, Turndorf et al. 1980).
- Merridew and colleagues (Merridew and Jones 1985) studied the effects of non-dependent lung $CPAP_5$ on arterial oxygenation. No change in cardiac output was demonstrated in the 3 patients in whom it was measured. No values for cardiac output were given in the article.
- Alfery and colleagues (Alfery, Benumof et al. 1981) found no difference in cardiac output if up to 15 cm H_2O of PEEP is applied to the non-dependent lung during one lung anesthesia in previously healthy dogs.
- Fujita and colleagues (Fujita, Yamasaki et al. 1993) demonstrated that during one lung anesthesia with ZEEP, $PEEP_5$ or $PEEP_{10}$ administered to the dependent lung, systemic hemodynamics were not altered from baseline.

The effects of initiation of one lung anesthesia on cardiac output and oxygen flux (where reported) can be summarized as follows:

1. At ZEEP either
   - No change in cardiac output occurs, or

- An increase in cardiac output, VO_2 and DO_2 and a decrease in SVR are seen.

2. On application of PEEP to the dependent lung
   - With up to 15 cm H_2O, no change in cardiac output has on occasion been measured;
   - However, these levels of PEEP are usually associated with a decrease cardiac output.
3. The combination of $PEEP_{10}$ /$CPAP_{10}$ consistently decreases cardiac output (Cohen, Eisenkraft et al. 1988; Cohen, Thys et al. 1985a).

	Cardiac output during OLA		
	No change	Decrease	Increase
ZEEP	Boldt, Muller et al. 1996; Fujita, Yamasaki et al. 1993; Malmkvist, Fletcher et al. 1989; Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Jenkins, Cameron et al. 1987; Carlsson, Bindslev et al. 1985; Rogers and Benumof 1985; Katz, Laverne et al. 1982; Rees and Wansbrough 1982a; Bachand, Audet et al. 1975; Bachand, Audet et al. 1975		Cohen, Eisenkraft et al. 1988
$PEEP_5$	Fujita, Yamasaki et al. 1993; Alfery, Benumof et al. 1981	Merridew and Jones 1985	
$PEEP_{10}$	Fujita, Yamasaki et al. 1993; Alfery, Benumof et al. 1981	Capan, Turndorf et al. 1980	
$PEEP_{15}$	Alfery, Benumof et al. 1981	Inomata, Nishikawa et al. 1997	
$CPAP_{10}$	Capan, Turndorf et al. 1980	Cohen, Thys et al. 1985b	Cohen, Eisenkraft et al. 1988
$PEEP_{10}$ / $CPAP_{10}$		Cohen, Eisenkraft et al. 1988; Cohen, Thys et al. 1985a	

Table 1.7.2.2.1 The effects of one lung anesthesia on cardiac output

1.7.3 Management of an acute increase in RV afterload during one lung anesthesia

1.7.3.1 Introduction

How is it possible to optimise the work of, and ultimately restore the efficiency of a right ventricle that is faced with an acute increase in afterload? On inspection of the diagram of ventricular-arterial coupling (Figure 1.5.2.10), it can be intuitively understood that improving the ratio of Ea to Ees (restoring the ratio to 1 to generate maximal stroke work or, optimally, restoring it to 0.5 to achieve maximal efficiency) will optimise the matching between the ventricle and its load. The theory of coupling defines the factors determining SV as being (Sagawa, Maughan et al. 1988):

$$SV = (Ees\ (Ved - Vo)) / (Ees + Ea) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 1.7.3.1.1}$$

Utilizing this approach, maximal SV may be achieved either by facilitating (Calvin, Jr. 1991):

1. A reduction of Ea and/or
2. An increase in Ees

Either of these manoeuvres will move the ventricle from a failing position on the SW or efficiency versus Ea curves, at least to a point where SW is maximal and the ventricle is better matched to its afterload. These variables may be addressed either singly or together. However, addressing one variable may influence another. For example, Fourie and co-workers have suggested that improving Ees of the right ventricle will be beneficial in optimising right ventricular coupling in acute pulmonary hypertension, not necessarily because of the increase in Ees, but because the improvement in ventricular elastance will match the new loading conditions (Fourie, Coetzee et al, 1992). An increase in stroke volume may be also, within limits, be facilitated by:

3. Optimising preload (Ved).

1.7.3.2 Optimising afterload during one lung anesthesia

During one lung anesthesia, the relative resistances of the dependent and non-dependent lung pulmonary vascular beds are of importance in determining shunt fraction and arterial oxygenation (Cohen, Eisenkraft et al. 1988). Minimizing the PVR of the dependent lung while minimally interfering with HPV in the non-dependent lung will optimise the total PVR. Optimising the PVR will further optimise distribution of blood between the lungs (Benumof 1991; Katz, Laverne et al. 1982; Benumof, Rogers et al. 1979). Little to no information is directly available in the literature regarding the factors that affect PVR to the dependent lung during one lung anesthesia. Conclusions regarding PVR have been derived from the reasoning that the degree of shunt and hypoxemia during one lung anesthesia is mostly related to the relative vascular resistances of the two pulmonary beds (Cohen, Eisenkraft et al. 1988).

The effects of various factors on PVR have been discussed previously, and only factors that are of relevance during one lung anesthesia will be discussed in this section.

1.7.3.2.1 Optimising lung volume during one lung anesthesia

Optimisation of dependent lung volume should minimize PVR and result in less of the cardiac output being shunted via the non-dependent lung (Cohen and Eisenkraft 1996; Benumof 1991; Katz, Laverne et al. 1982). Atelectasis may be due to an increased closure of small airways caused by a decrease in the FRC (Cohen and Eisenkraft 1996).

Ventilating the dependent lung with a tidal volume that is too small (less than 10 $ml.kg^{-1}$) may predispose to atelectasis and an increase in PVR (Benumof 1991; Kerr, Smith et al. 1974). Therefore, using large tidal volumes comprising either 16% of the total lung capacity, or 15 to 20 $ml.kg^{-1}$, have been suggested to recruit alveoli, increase the FRC and prevent closing capacity from exceeding the FRC (Cohen and Eisenkraft, 1996; Inomata, Nishikawa et al, 1997; Benumof, 1991). However, the use of such large tidal volumes to ventilate the dependent lung has not been shown to have major beneficial effects on either oxygenation or PVR (Cohen and Eisenkraft 1996; Benumof 1991; Katz, Laverne et al. 1982). On the other hand, the use of an excessively large tidal volume has been associated with an increase in FRC and PVR that may increase diversion of blood to the non-dependent lung (Cohen and Eisenkraft 1996; Benumof 1991):

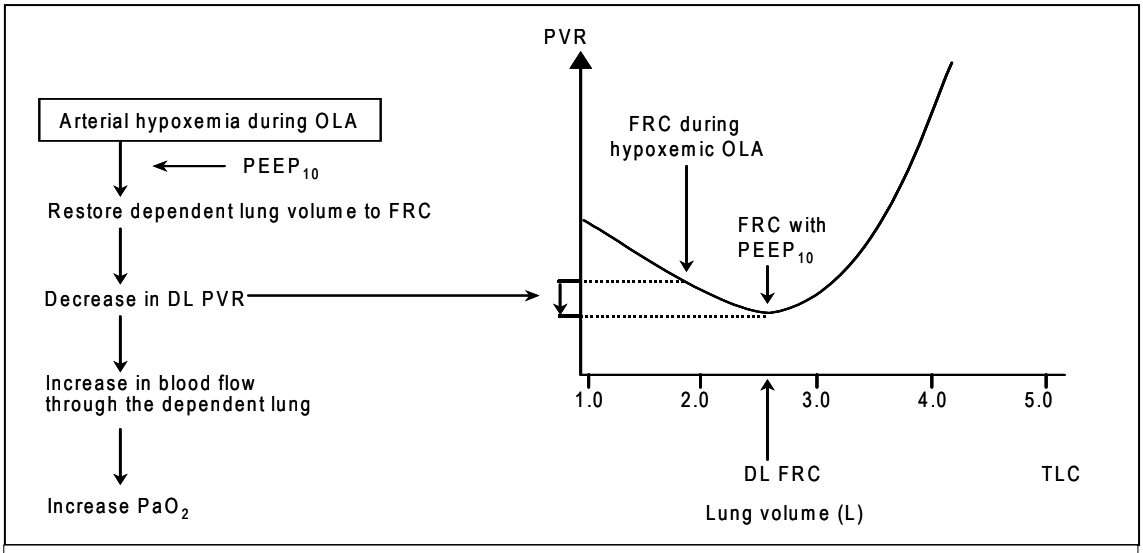


Figure 1.7.3.1. The effect of PEEP on the dependent lung during one lung anesthesia in the lateral decubitus position. See text for details. Adapted from Cohen, 1995

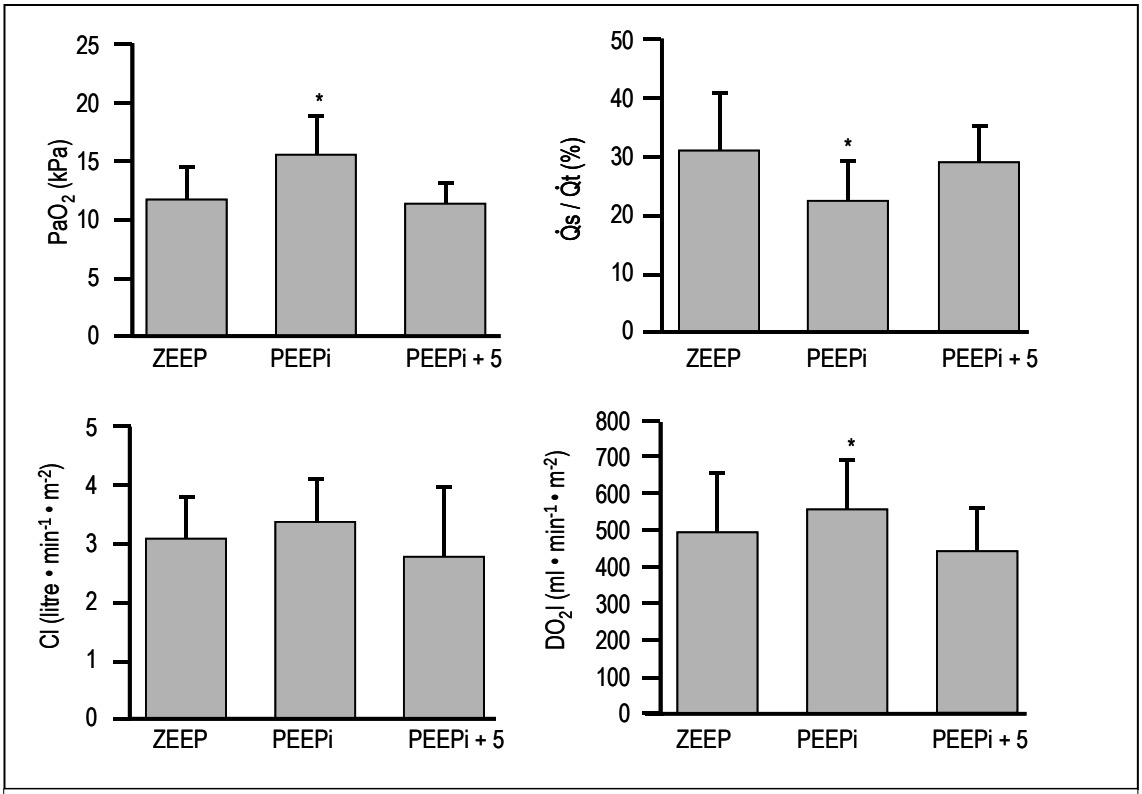


Figure 1.7.3.2. The effect of different levels of PEEPi and PEEPe applied to the dependent lung (see text for details) The correct level of PEEP may benefit the FRC with beneficial effects on shunt, oxygenation, and cardiac output. However the therapeutic window is narrow, and excessive levels may prove deleterious. ZEEP indicates one lung ventilation with no added PEEPe, PEEP I indicates IPPV with PEEPe equivalent to PEEP1, and PEEPi + 5 indicates that 5 mm Hg of PEEP was added to the previous level of PEEPi that was being used too ventilate the DL. Redrawn from Inomata et al, 1997

- The application of PEEP to the dependent lung is a logical manoeuvre in an attempt to ensure that FRC and PVR are maintained within normal limits and prevent alveolar and small airway closure (Cohen and Eisenkraft 1996; Benumof 1991; Cohen, Eisenkraft et al. 1988; Cohen, Thys et al. 1985b; Katz, Laverne et al. 1982; Tarhan and Lundborg 1970). The application of $PEEP_{10}$ to the dependent lung has however produced variable results on oxygenation, frequently resulting in an increase (Cohen and Eisenkraft 1996; Cohen, Thys et al. 1985b; Katz, Laverne et al. 1982; Capan, Turndorf et al. 1980; Tarhan and Lundborg 1970) but also no change (Cohen and Eisenkraft 1996; Cohen, Eisenkraft et al. 1988; Lowenstein, Johnston et al. 1983; Katz, Laverne et al. 1982; Aalto, Heinonen et al. 1975) in the shunt fraction during one lung ventilation. The question arises therefore, as to the level of PEEP that needs be applied to optimise lung volumes and maintain PVR at its lowest level in the dependent lung? Cohen and Eisenkraft, (Cohen and Eisenkraft 1996), and Inomata and colleagues (Inomata, Nishikawa et al. 1997) have addressed this problem.

- Inomata and colleagues (Inomata, Nishikawa et al. 1997) studied the effect of intrinsic PEEP and externally applied PEEP to the dependent lung on right ventricular function. The patients had normal preoperative lung function tests. Their dependent lungs were ventilated via a 37 French gauge left sided Mallinckrodt ® DLT with a tidal volume of 8 $ml.kg^{-1}$ at a rate of 16 breaths per minute with an ratio of inspiratory to expiratory time (I.E. ratio) of 1:2. At first, the DL's were ventilated with ZEEP while PEEPi was measured. PEEPi was measured as being 4 ± 2 mm Hg during OLA. Thereafter, external PEEP equal to the patients individually measured PEEP was delivered to the DL. This manoeuvre resulted in an increase in RVEF, cardiac index, and oxygen delivery and was accompanied by a decrease in shunt and improvement in arterial oxygenation, compared to when only PEEPi was present. However, application of a further 5 mm Hg of PEEP to the dependent lung resulted in an increase PVR to values greater than those observed with ZEEP (from 208 ± 64 to 286 ± 109 $dynes.sec.cm^{-5}.m^{-2}$), and decreases in cardiac index, delivery of oxygen and RVEF. Shunt increased to values close to those seen at ZEEP. The patients studied by Inomata had no clinical evidence of COPD or restrictive lung disease, and unfortunately does not provide us with a blanket answer to the problem of how to optimise lung volume and minimize PVR in the individual patient. It does however emphasize the narrow therapeutic window seen with PEEP and the need to individualize therapy (Conacher 1998; Inomata, Nishikawa et al. 1997).

- Cohen and Eisenkraft, demonstrated that $PEEP_{10}$ improved oxygenation only in patients with low a PaO_2 during one lung anesthesia (Cohen and Eisenkraft 1996; Cohen 1995; Cohen, Thys et al. 1985b). They "*postulate that the patient who's PaO_2 is low while on one lung ventilation has an end-expiratory lung volume that is less than ideal and a high PVR. The application of $PEEP_{10}$ increases lung volume, restores FRC to normal, decreases PVR, and improves blood flow through (the dependent lung), all of which result in an increase in PaO_2 (Cohen and Eisenkraft 1996). Conversely, in a patient whose PaO_2 on one lung ventilation is greater than 80 mm Hg (i.e. not hypoxic), the application of $PEEP_{10}$ increases the existing favourable ventilation perfusion ratio, and the increase in FRC causes a decrease in PaO_2 because of increases in PVR and shunt*" (Figure 1.7.3.1) (Cohen and Eisenkraft 1996).

- Slinger and colleagues studied whether improved oxygenation occurs when the application of external PEEP causes the plateau end-expiratory pressure to move towards the lower inflexion point of the compliance curve (Slinger, Kruger et al. 2001). They showed that on the application of $PEEP_5$, if the plateau end-expiratory pressure moved toward the lower inflexion point, oxygenation improved. Lung volume can be inferred from the lower inflexion point on the compliance curve (Nunn 1987; Slinger, Kruger et al. 2001). Therefore, if $PEEP_5$ increases lung volume towards FRC during OLA, oxygenation will increase. However, if on the application of $PEEP_5$, the plateau end-expiratory pressure moved away from the lower inflexion point, then oxygenation decreased. This may be explained as follows: if $PEEP_5$ increases lung volume above FRC, PVR may increase and blood will be diverted to the NDL with a resultant increase in shunt fraction. It is suggested that the discrepancy in results between various studies following on the application of $PEEP_5$ to the DL is because $PEEP_5$ may have different effects on lung volume in different patients. Intrinsic PEEP and externally applied PEEP interact in an unpredictable fashion during OLA to produce increases in lung volume (Slinger, Kruger et al. 2001).

The efficacy of adjustments to tidal volume and PEEP in restoring and maintaining dependent lung FRC and minimizing PVR may depend on the initial DL FRC (Figure 1.7.3.1). Nonetheless, the variable results of these manoeuvres leads to the consensus that the therapeutic window to maintain dependent lung volume, minimize PVR and reduce shunting during one lung ventilation, is narrow (Figure 1.7.3.2) (Inomata, Nishikawa et al. 1997; Cohen and Eisenkraft 1996; Benumof 1991).

Another method of favourably diverting blood between the two pulmonary beds is to compress or occlude the pulmonary flow through the NDL vascular bed (Ishikawa, Nakazawa et al. 2003).

Application of $PEEP_{10}$/$CPAP_{10}$ has been shown to improve arterial oxygenation but at the same time decrease both cardiac output and oxygen delivery (Cohen, Eisenkraft et al. 1988). It is noteworthy that the beneficial effect of $PEEP_{10}$/$CPAP_{10}$ on oxygenation is *not* because it increases PVR and thereby diverts blood flow away from the non-dependent lung as it has been demonstrated not to affect total PVR (Cohen and Eisenkraft 1996; Alfery, Benumof et al. 1981). There are no reports of its influence on right ventricular function.

1.7.3.2.2 Hypoxic pulmonary vasoconstriction

Factors affecting HPV in the non-dependent lung during one lung anesthesia have already been addressed. A low P_AO_2 will induce HPV in the dependent lung, which is most undesirable. The individual factors on which P_AO_2 is dependent are summarized in the alveolar gas equation:

$$P_AO_2 = (P_BO_2 - PH_2O)\ FiO_2 - (P_ACO_2 / \text{respiratory quotient}) \quad \text{Equation 1.7.3.2.2.1}$$

Administering 100% oxygen at sea level may optimise FiO2. Ventilation of the dependent lung may be optimised by:

- Maintaining an ideal position on the pressure-volume relationship, thereby optimising lung compliance and,
- Decreasing airway resistance (removing secretions, optimal placement of the correct size DLT, optimising reversible airway resistance components of obstructive airways disease).

Additionally, maintaining ideal lung volume will optimise factors preventing the deleterious effects of HPV in the dependent lung:

- Optimal ventilation perfusion matching will be maintained. Lung units with low V/Q ratios will have a low P_AO_2. Low alveolar oxygen partial pressures will induce HPV that limit the shunt fraction. The effect of this on dependent lung PVR will depend on the rate of flow of blood through, and the vascular reserve of that lung.
- Excessive increases in lung volume may lead to both increases in PVR and decreases in venous return. Both may lead to a decrease in cardiac output. A decrease in cardiac output may lead to greater tissue extraction of oxygen and a lower P□O_2 with generalized HPV in the dependent lung.

Rees and Wansbrough have demonstrated that no change in total PVR or mean PAP occurred if oxygen was insufflated down the non-dependent lung (Rees and Wansbrough 1982a). Nonetheless, shunt was less and PaO_2 greater in the patients in which oxygen was insufflated down the non-dependent lung (Cohen 1995; Rees and Wansbrough 1982a).

1.7.3.2.3 Pulmonary vasodilator drugs during lung surgery

The multiple attempts to use various non-selective pulmonary vasodilators during pulmonary hypertension (prostaglandins, hydralazine, nitrates, sodium nitroprusside, adenosine, captopril, non-steroidal anti-inflammatory agents, prostacyclin, calcium channel blockers) attest to the problems involved in their use (Stoltzfus 1997; Haraldsson, Kieler Jensen et al. 1996; Pearl and Siegel 1992; Bolliger, Fourie et al. 1991; Lake 1990; Melot, Lejeune et al. 1989; Prielipp, Rosenthal et al. 1988; Packer, Medina et al. 1985; D'Ambra, LaRaia et al. 1985; Hasselstrom, Eliasen et al. 1985; Parsons and Wetzel 1985; Weigelt, Gewertz et al. 1982):

- Use of these drugs, except for aminophyline and hydralazine, will lead to inhibition of HPV and hypoxemia. Therefore their use during one lung anesthesia may present problems (Myles, Weeks et al. 1997).
- Vasodilators may decrease RVEDV that may result in decreases in RVSWI and cardiac output (Parsons and Wetzel 1985).(Sibbald, Short et al. 1985)
- In ALI, fixed anatomical lesions (thrombi) in the pulmonary vasculature may be unresponsive to vasodilators (Troncy, Francoeur et al. 1997).
- Even the nitric oxide donors (nitroglycerine and sodium nitroprusside) are not selective at higher dosages for the pulmonary vasculature and cause systemic hypotension. A decrease in coronary perfusion pressure is deleterious to the right ventricle facing an increase in afterload. Adenosine and prostaglandin E1, when compared to the other pulmonary vasodilators, appear to elicit the greatest decrease in PVR relative to the decrease in SVR (Prielipp, Rosenthal et al. 1988). However, adenosine and prostaglandin E1 also give rise to systemic hypotension (Bolliger, Fourie et al. 1991)(Fullerton, Jones et al. 1996)

Nevertheless, inhaled nitric oxide is a selective pulmonary vasodilator that has little effect on systemic hemodynamics. In response to an editorial by Zapol in 1994 in which he suggested that that the use of nitric oxide be investigated during one lung anesthesia, Wilson, Kapelanski et al, (Wilson, Kapelanski et al. 1997) administered 40 parts per million of nitric oxide to 6 patients with a variety of lung pathologies undergoing OLA. No difference in PVR, PAP, cardiac output or oxygenation was found whether nitric oxide was administered or not during one lung anesthesia. The function of the right ventricle during nitric oxide administration while OLV was being conducted was

not specifically studied. As the pulmonary vasodilator potency of inhaled nitric oxide is directly proportional to the PVR before administration of the drug, their findings are not unexpected as the patients that were studied had normal PVR before and during OLA. Based on their study, Wilson and colleagues did not advocate the use of nitric oxide during one lung anesthesia in subjects who experience hypoxia and in whom PVR is not elevated (Wilson, Kapelanski et al. 1997).

1.7.3.2.4 The effect of anesthesia and surgery on pulmonary vascular resistance

Individual anesthetic agents and the interaction of anesthesia, surgery and the sympathetic nervous system may affect the pulmonary vasculature. The effect of anesthesia on HPV has already been addressed. Albeit that anesthetic agents minimally affect PVR during two-lung ventilation, isoflurane has been shown to cause pulmonary vasodilatation (Wilson, Kapelanski et al. 1997; Burrows, Klinck et al. 1986; Mathers, Benumof et al. 1977). Large dosages of alfentanil and other opioids do not appear to have an effect on the pulmonary vasculature (Armstrong 1992; Burrows, Klinck et al. 1986). A high dose opioid technique administered in combination with IAA has been shown to decrease sympathetic nervous system tone. Decreased sympathetic nervous system stimulation decreases baseline PVR whereas stimulation of sympathetic nerves has been demonstrated to increase PVR (Pagel, Fu et al. 1998; Wilson, Kapelanski et al. 1997; Armstrong 1992; Burrows, Klinck et al. 1986; Nimbkar and O'Neill 1973; Kadowitz and Hyman 1973).

1.7.3.3 Optimising right ventricular preload

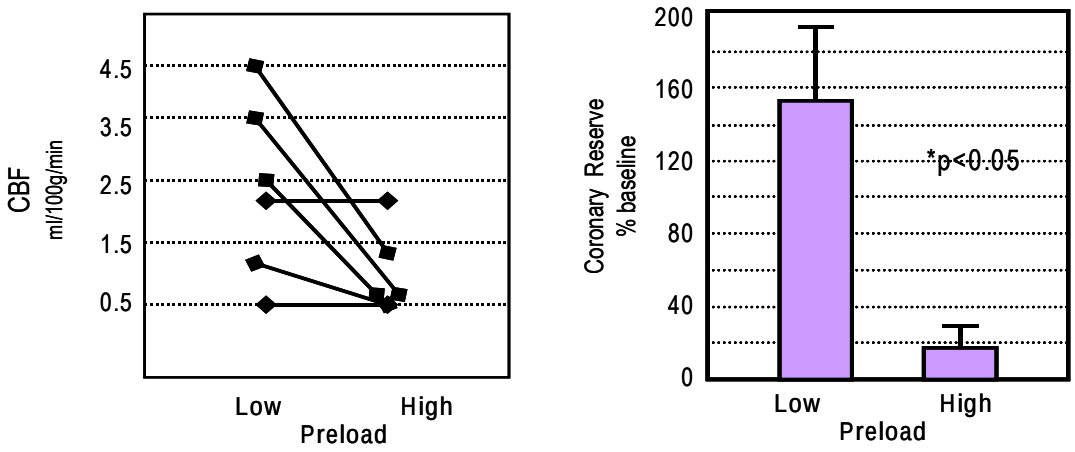
Augmenting EDV will potentially maximize the stroke work outputted by a ventricle with decreased contractility (Sibbald and Driedger 1983). Animal experiments on right ventricular infarction conducted between 1974 and 1985 (Dell'Italia, Starling et al. 1985; Guiha, Limas et al. 1974; Cohn, Guiha et al. 1974) lead to the recommendations that the first response to a decrease in right ventricular SV should be to administer fluid intravenously, thereby increasing RVEDV and sarcomere length (Jacobsohn, Chorn et al. 1997; Stoltzfus 1997; Hines and Barash 1993; Dhainaut and Squara 1992; Calvin, Jr. 1991; Dell'Italia, Starling et al. 1985; Sibbald and Driedger 1983).

However, volume expansion in patients with a decrease in right ventricular SV due to an increase in RV afterload has not been shown to produce uniformly beneficial effects (Dell'Italia, Starling et al. 1985). One the one hand, intravascular volume expansion has been shown to maintain cardiac output in acute pulmonary hypertension (Wiedemann and Matthay 1997; Sibbald and Driedger 1983). On the other hand, various studies have echoed the fact that volume loading of the right ventricle faced with an increase in afterload may not only be unsuccessful but injurious (Goldhaber 1997; Stoltzfus 1997; Schreuder, Schneider et al. 1988; Ghignone, Girling et al. 1984; Prewitt and Ghignone 1983; Milnor 1982c). Ghignone and colleagues demonstrated that volume-loading patients with right ventricular dysfunction resulted in marked deterioration of RV performance, and RV stroke volume and systemic mean arterial pressure were shown to decrease (Ghignone, Girling et al. 1984). Canine pulmonary embolism resulting in circulatory insufficiency, when treated with volume therapy alone, resulted in the death of all dogs (Stoltzfus 1997). A differentiating factor as to when volume loading may or may not be successful has been suggested to be the resistance faced by the right ventricle. When PVR was less than 12 mm Hg.litre^{-1}.minute^{-1}, volume therapy usually increased cardiac output. However when PVR was greater than 12 mm Hg.litre^{1}.minute^{-1}, volume infusion usually resulted in a decrease in cardiac output. The RVEDP's at which this decrease in cardiac output has been reported to occur, 7 mm Hg (Prewitt and Ghignone 1983) or 11.9 mm Hg (Ghignone, Girling et al.

1984), were surprisingly low. This differentiation does not however consider the contractility of the right ventricle.

The mechanism whereby cardiac output does not increase in response to fluid therapy is suggested to be due to:

- The damaged right ventricle operating on the flat part of its ventricular function curve (Dell'Italia, Starling et al. 1985): volume loading will not increase cardiac output or RVSWI (Stoltzfus 1997; Dell'Italia, Starling et al. 1985) and may even position the ventricle on the descending part of the ventricular function curve (Prewitt and Ghignone 1983).
- The increase in right ventricular cavity size and pressure may produce extremes of the so-called "parallel" ventricular interaction (Dell'Italia, Starling et al. 1985; Ghignone, Girling et al. 1984; Milnor 1982c). This leads to impairment of the left ventricular performance (Dell'Italia, Starling et al. 1985).
- Increases in intracavitary pressure and radius will increase wall stress of the right ventricle (Wiedemann and Matthay 1997; Stoltzfus 1997; Ghignone, Girling et al. 1984; Prewitt and Ghignone 1983; Sibbald and Driedger 1983; Korr, Gandsman et al. 1982; Milnor 1982c). This leads to two deleterious effects. Firstly, the acute rise in right ventricular afterload due to the increase in radius will decrease right ventricular stroke volume (Korr, Gandsman et al. 1982). This has been shown through series diastolic ventricular interaction, to decrease systemic arterial pressure (Dell'Italia, Starling et al. 1985). Secondly, decreases in RV subendocardial blood flow (Figure 1.3.3.1) (Dyke, Brunsting et al. 1987) followed by frank RV myocardial



	Low preload	High preload	
RVEDP	3	10	mmHg
RV systolic pressure	32	53	mmHg
Systemic mean arterial pressure	50	51	mmHg

Figure 1.7.3.3.1 Decrease in RV subendocardial blood flow and coronary vascular reserve as preload is increased from a low to a low level. Note that "low level" means 3 mm Hg and "high level" of preload means 10 mm Hg. Both high and low levels are considered relatively moderate filling pressures in acute RV failure. Reproduced from Dyke, Brunsting et al. 1987.

ischemia may be induced by rapid increases in preload (Wiedemann and Matthay 1997; Stoltzfus 1997; Ghignone, Girling et al. 1984; Prewitt and Ghignone 1983; Sibbald and Driedger 1983; Milnor 1982c).

- The development of tricuspid incompetence will limit forward stroke volume especially in the presence of an increase in opposition to RV ejection (Wiedemann and Matthay 1997).

Because right ventricular performance has been shown to deteriorate with volume administration at relatively low RV end-diastolic pressures (7 to 12 mm Hg), RV filling pressures may be a poor predictor of the response to volume loading when a low cardiac output is caused by an increase in RV afterload (Calvin, Jr. 1991; Ghignone, Girling et al. 1984). The great compliance of the right ventricle allows large volume increases which are accompanied by unimpressive rises in end-diastolic pressure until the elastic limits set by the pericardium are reached (Milnor 1982c). Guidelines as to fluid administration utilizing right-sided filling pressures are therefore problematic in the face of acute PHPT. Some authors suggest that fluid administration should be started if CVP is less than 10 mm Hg (Dodson, Nathan et al. 1997); others suggest that the volume administration is used to increase end-diastolic pressure by at least 5 mm Hg and RVEDP should not exceed 20 mm Hg (Dell'Italia, Starling et al. 1985).

Volume therapy during pulmonary hypertension is best guided by monitoring RVEDV, indices of RVEDP, position of the interventricular septum, cardiac output and P□O_2 utilizing both a pulmonary artery catheter (PAC) and echocardiography (Stoltzfus 1997; Lichtwarck-Aschoff, Leucht et al. 1994; Rafferty, Durkin et al. 1993; Vincent, Thirion et al. 1986). Volume therapy should be aimed to increase cardiac output rather than filling pressures as:

- Excessive volume administration may cause a decrease in cardiac output.
- Indices of left ventricular filling such as LVEDP or PAWP, because of ventricular interdependence, may not reflect true volume of the LV during right ventricular dysfunction (Dell'Italia, Starling et al. 1985; Prewitt and Ghignone 1983; Laver, Strauss et al. 1979).
- CVP values are also not considered by some to be useful as a guide to volume therapy in the presence of an increase in right ventricular afterload (Stoltzfus 1997).

It is apparent that caution needs to be applied when utilizing fluid loading in the approach to therapy of RV dysfunction. A clear difference in approach to maximizing preload exists, based on the origin of the decrease in RV stroke volume (Fourie, Coetzee et al. 1992b; Prewitt and Ghignone 1983). Most studies would support the initial moderate use of volume therapy in the face of pulmonary hypertension but it should be much more cautiously titrated in those subjects with greater increases in right ventricular afterload than those with myocardial problems and normal afterload. The difference appears to occur at a PVR of more than 12 mm Hg.litre^{1}.minute^{-1} (Stoltzfus 1997; Prewitt and Ghignone 1983).

Furthermore during one lung anesthesia, additional factors need to be considered with regard to fluid therapy:

- Vasodilatation and myocardial depression on induction of anesthesia may necessitate fluid administration;
- Third space and blood loss;
- The deleterious effects of IPPV and PEEP on venous return and,
- The risk of postoperative pulmonary edema that carries a high mortality (Slinger 1995).

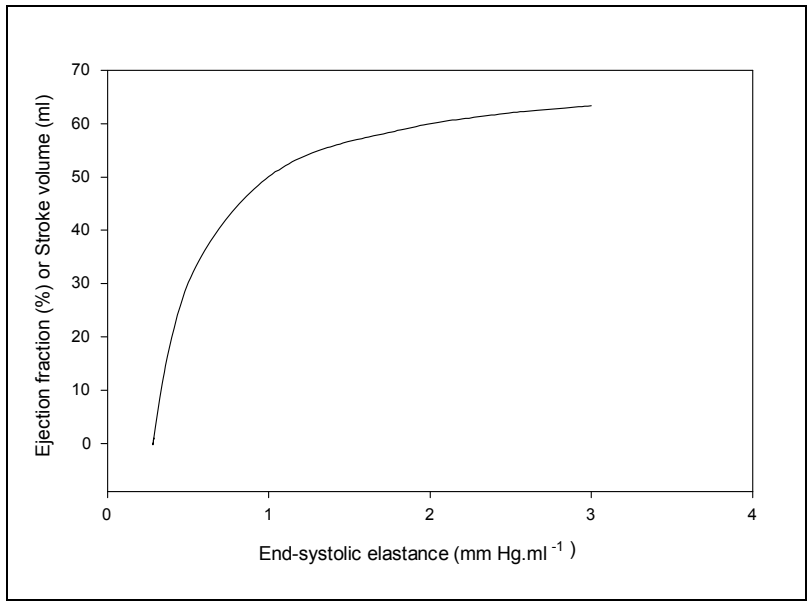


Figure 1.7.3.4.2 Relationship of RV stroke volume and RV ejection fraction to end-systolic elastance at a constant RVEDV (100 ml), Vo (5 ml), and Pes (20 mm Hg). This relationship was constructed using Equation 1.7.3.1.1 and EF = 1 – ((Vo+Pes/Ees)/RVEDV)).

Adapted from Sunagawa, Maughan et al. 1988

1.7.3.4 Optimising the inotropic state of the right ventricle

1.7.3.4.1 Avoidance of excessive myocardial depression by anesthesia

It is prudent to avoid excessive myocardial depression, as this will inhibit the ability of the right ventricle to generate a greater stroke work in the face of an increase in afterload. A high dose opioid technique in addition to judicious dosages of inhalation agent (< 1 MAC isoflurane) should avoid this problem in hearts with reasonable ventricular function (Heerdt, Gandhi et al. 1998).

1.7.3.4.2 Inotropic support

Optimising preload alone may prove inadequate or inappropriate in optimising RV performance in the face of an increase in afterload (Hines and Barash 1993). Optimising coupling of the right ventricular and its afterload may therefore involve increasing contractility. The advantages of increasing contractility are as follows:

1. An increase in Ees will increase the load with which the ventricle can cope before it fails (Figures 1.5.2.8, 1.5.2.9 and 1.5.2.10).
2. Using Equation 1.7.3.1.1, the relationship between stroke volume and end-systolic elastance at constant values of end-diastolic volume, Vo and end-systolic pressure of the ventricle can be plotted (Figure 1.7.3.4.2). If Pes and preload are unchanged, stroke volume and ejection fraction increase hyperbolically with increases in Ees. Note that on the one hand, a reduction in end-systolic elastance from the normal value causes a dramatic decreases in stroke volume and ejection fraction. On the other hand, increases in end-systolic elastance do not result in significant increases in stroke volume or ejection fraction (Sagawa, Maughan et al. 1988).
3. Increases in stroke volume and cardiac output will result in an increase in oxygen delivery and increase in P□O_2 that may have advantages in the presence of the significant shunt that exists during one lung anesthesia. Suitable positive inotropic agents in the scenario of one lung anesthesia should not possess

adverse and even possess favourable effects on PVR (Mathru, Dries et al. 1990).

Few systematic studies of the use of inotropes during increases in right ventricular afterload or OLA have been conducted.

1.7.3.4.3 Inodilators

Zapol and Snider originally described the use of isoprotenolol infusions in patients with ALI and acute pulmonary hypertension in the hope that it would cause pulmonary vasodilatation while providing inotropic support (Prewitt and Ghignone 1983; Aalto-Setala, Heinonen et al. 1975). Canine studies of pulmonary embolism have shown the failure of isoprotenolol to improve RV function. Human literature describing the use of isoprotenolol has mostly consisted of anecdotal reports of the use of the drug for right ventricular failure after cardiopulmonary bypass (CPB). The problems of systemic vasodilatation, hypotension, tachycardia and hypoxemia associated with the use of this drug may lead to a decrease in CPP and ischemia of the stressed right ventricle (Hines and Barash 1993).

The phosphodiesterase inhibitors are described as having both vasodilator and inotropic properties and have been suggested to be of use during acute right ventricular dysfunction and pulmonary hypertension (Chen, Bittner et al. 1997; Stoltzfus 1997; Lee and Hou 1995; Petry and Dutschke 1994; Deeb, Bolling et al. 1989; Konstam, Cohen et al. 1986). An increase in cardiac index and a decrease in PVR typically occurs with the use of these agents (Chen, Bittner et al. 1997; Stoltzfus 1997; Konstam, Cohen et al. 1986). Furthermore, they have been shown to potentiate the inotropic effects of the beta-adrenergic agonists (Doyle, Dhir et al. 1995). On their own they do not produce much decrease in systemic arterial pressure, an important consideration in the presence of right ventricular dysfunction (Doyle, Dhir et al. 1995).

The beneficial effect of amrinone and milrinone on RV function has been suggested to be secondary to their powerful pulmonary vasodilator effects (Chen, Bittner et al. 1997; Lee and Hou 1995; Doyle, Dhir et al. 1995; Petry and Dutschke 1994; Lake 1990; Deeb, Bolling et al. 1989; Konstam, Cohen et al. 1986). Other authors (Chen, Bittner et al. 1997; Doyle, Dhir et al. 1995; Petry and Dutschke 1994) attribute the increase in cardiac output seen with the phosphodiesterase inhibitors to increases in contractility and do not attribute any effect to reduction in afterload (Chen, Bittner et al. 1997; Petry and Dutschke 1994). The discrepancy for the reasons given why right ventricular function improves with these drugs may lie therein that they decrease PVR to a greater degree in those patients with the highest baseline PVR (Stoltzfus 1997; Doyle, Dhir et al. 1995; Petry and Dutschke 1994). Phosphodiesterase inhibitors have been shown to improve coupling of the RV to its load (Chen, Bittner et al. 1997).

Dobutamine has shown to improve RV-PA matching, and may prove to be more useful than volume loading during states of acute pulmonary hypertension (Calvin 1998; Dell'Italia, Starling et al. 1985; Ghignone, Girling et al. 1984). Dobutamine does not however appear to be a selective pulmonary vasodilator: much of the decrease in calculated PVR is secondary to an increase in cardiac output accompanied by little increase in PA pressure due to pulmonary vascular recruitment and dilatation that occurs in relatively normal pulmonary vascular beds (Wolfer, Krasna et al. 1994; Dell'Italia, Starling et al. 1985). Coddens and colleagues (Coddens, Delooft et al. 1993) have demonstrated a decrease in pulmonary Ea, but not pulmonary vascular resistance during dobutamine administration. They found that RVEF correlated best with Ea and PAWP and suggest that this underscores the importance of LV function in

determining right ventricular afterload (Coddens, Delooft et al. 1993). Furthermore, concerns regarding an increase in shunt fraction with the administration of dobutamine during OLA have recently been questioned (Mathru, Dries et al. 1990). On this point, Domino emphasizes that PaO_2 is often well preserved when dobutamine is administered to critically ill patients because of the improvement in cardiac output (Domino 1997; Renard, Jacobs et al. 1984). Stolftzfus pointed out another aspect of the use of dobutamine in RV dysfunction. He suggests that a more marked increase in heart rate is seen when utilizing dobutamine for primary right ventricular dysfunction than when it is used for left ventricular dysfunction (Stoltzfus 1997; Imai, Saitoh et al. 1992).

1.7.3.4.4 Inoconstrictors and vasoconstrictors

One of the final pathways in right ventricular decompensation is right ventricular ischemia. Restoration of aortic pressure and thereby maintenance of coronary perfusion pressure is necessary for preservation of RV function (Coyle, Carlin et al. 1990; Schreuder, Schneider et al. 1989; Ghignone, Girling et al. 1984; Prewitt and Ghignone 1983; Vlahakes, Turley et al. 1981). The inoconstrictors comprise drugs with both inotropic and vasoconstrictor (α adrenergic agonist) properties. An increase in inotropicity will benefit the RV faced with an increase in afterload. However, two questions need to be examined when using agents with vasoconstrictor properties. Firstly, do inoconstrictors benefit RV function by virtue of their increase in coronary perfusion pressure (systemic aortic pressure) and secondly, are the benefits of an increase in Ees offset by a deleterious increase in PVR (Coyle, Carlin et al. 1990)?

Right ventricular (RV) function and pulmonary hemodynamics were studied in burned patients while administering up to 9.0 micrograms.kg^{-1}.min^{-1} of dopamine (Martyn, Wilson et al. 1986). No significant improvement in RV performance (RVEDV, RVEF) was observed. However, with the infusion of dopamine, elevations in mean pulmonary artery pressures were noted, particularly in patients with pre-existing pulmonary artery hypertension (Martyn, Wilson et al. 1986). Concern about these deleterious effects on pulmonary vascular resistance, prompted studies comparing the effects of dobutamine and dopamine on the pulmonary circulation (Stoltzfus 1997). Imai and colleagues (Imai, Saitoh et al. 1992) demonstrated lower PVR with dobutamine than with similar dosages of dopamine (10 to 20 ug.kg^{-1}.min^{-1}), whereas Vincent et al, (Vincent, Reuse et al. 1988) found no difference at a dose of 5 ug.kg^{-1}.min^{-1}. However, even at dosages of dopamine (5 ug.kg^{-1}.min^{-1}) that did not increase PVR, similar dosages of dobutamine resulted in more favourable effects on right ventricular function (Table 1.7.3.4.4.1) (Stoltzfus 1997; Vincent, Reuse et al. 1988). It appears that patients with pre-existing pulmonary hypertension who received higher dosages of dopamine, experience greater increases in PVR. The explanations brought forward are:

- In equipotent dosages, dopamine has more prominent alpha adrenergic effects while dobutamine has stronger beta adrenergic effects,
- Coronary blood flow has been shown to be greater with dobutamine than dopamine (Vincent, Reuse et al. 1988). Furthermore, dopamine has been suggested to have unfavourable effects on right ventricular oxygen supply-demand relationship with decreases in RVEF in spite of the restoration of right ventricular perfusion pressure (Schreuder, Schneider et al. 1989) and,
- The use of dopamine has been associated with an increase in LV filling pressures. LV filling pressures either do not change or decrease with dobutamine administration (Vincent, Reuse et al. 1988). PAWP may play an important role in determining pulmonary vascular resistance (Coddens, Delooft et al. 1993).

No studies have been conducted as to the effects of adrenaline on right ventricular function in the face of an increased afterload (Stoltzfus 1997). Lowenstein and colleagues published a case report of the beneficial effect of adrenaline in 5 patients with heparin-protamine reactions (Lowenstein, Johnston et al. 1983). In a study of patients in severe septic shock, adrenaline administration proved beneficial in patients with right ventricular failure unresponsive to fluid, dopamine and dobutamine (Le Tulzo, Seguin et al. 1997). Right ventricular function improved in spite of an 11% increase in pulmonary artery pressure (Le Tulzo, Seguin et al. 1997).

	Dopamine	Dobutamine	Significance
Stroke index (ml.m^{-2})	28.1 ± 3.6	31.0 ± 3.8	p<0.01
PAWP (mm Hg)	15.1 ± 1.0	13.9 ± 1.2	p<0.05
RAP (mm Hg)	14 ± 1.3	12.2 ± 1.1	p<0.05
RVEF %	21.5 ± 2.7	23.7 ± 2.9	p<0.01
RVEDVI (ml)	140 ± 12	141 ± 12	not significant
MAP (mm Hg)	88	85	not significant
PAP (mean) (mm Hg)	29.4 ± 8.8	28.4 ± 9.3	not significant

Table 1.7.3.4.4.1 Effects on RV function of a change from dopamine to dobutamine in critically ill patients without hypotension. 15 subjects were included in the study. (Vincent, Reuse et al. 1988).

The use of noradrenaline has been shown to markedly improve function of the failing RV in the presence of an increase in RV afterload (Stoltzfus 1997; Myles, Weeks et al. 1997; Raffin, Michel-Cherqui et al. 1992; Coyle, Carlin et al. 1990; Schreuder, Schneider et al. 1989; Schneider, Groeneveld et al. 1987; Ghignone, Girling et al. 1984). In some studies, noradrenaline has resulted in a decrease in PVR; however in other studies PVR did not increase, albeit that there was an increase in mean PAP secondary to an increase in cardiac output (Kwak, Lee et al, 2002; Stoltzfus 1997; Ghignone, Girling et al. 1984; Angle, Molloy et al. 1989). Schreuder and colleagues suggested that the increase in PVR in their study was offset by a concomitant improvement in right ventricular myocardial oxygen demand–supply relationship (Schreuder, Schneider et al. 1989). Furthermore, they described a positive correlation between RVEF and RV coronary perfusion pressure with the use of noradrenaline (Schreuder, Schneider et al. 1989). An interesting approach to the problem of pulmonary vasoconstriction associated with noradrenaline administration is to infuse the drug into the left atrium (Coyle, Carlin et al. 1990). The peripheral vasculature clears 40% of the infused noradrenaline, compared to the 84% cleared by the pulmonary circulation. This results in significantly less pulmonary vasoconstriction.

Phenylephrine will induce peripheral vasoconstriction and increase right ventricular coronary perfusion pressure. In

a landmark study, Vlahakes and colleagues (Vlahakes, Turley et al. 1981) demonstrated that an increasing coronary perfusion pressure using phenylephrine reversed right ventricular failure in an animal model of pulmonary hypertension. Other sources also suggest that PVR may not be greatly affected by phenylephrine (Kozhevnikov, Glonti et al. 1992; Meadow, Rudinsky et al. 1986) (abstracts only). A study done in humans with chronic pulmonary hypertension (mean PAP 58 mm Hg) who were administered phenylephrine, demonstrated an increase in RV perfusion pressure but worsening of right ventricular function secondary to pulmonary vasoconstriction (Stoltzfus 1997; Rich, Gubin et al. 1990). Their conclusion was that phenylephrine might not be of benefit in this scenario: however it must be noted that these patients did not have pre-existing hypotension (Rich, Gubin et al. 1990). Lake suggests that albeit phenylephrine and other alpha agonists increase PVR, they are useful in restoring right ventricular perfusion pressure (Lake 1990). Differences in PVR recorded in various studies when vasopressors are administered, may be due to differences in:

- The pre-existing pulmonary vascular tone (Kozhevnikov, Glonti et al. 1992; Coyle, Carlin et al. 1990; McMurtry, Rodman et al. 1988);
- Differences between species (McMurtry, Rodman et al. 1988);
- Down regulation of pulmonary alpha receptors (Coyle, Carlin et al. 1990) and,
- Dose and route of administration (Coyle, Carlin et al. 1990; McMurtry, Rodman et al. 1988).

It should be noted that sympathetic nervous system stimulation has been demonstrated to induce pressure gradients of 20 to 40 mm Hg across the normal right ventricular outflow tract (Pace, Keefe et al. 1969). The influence of this on right ventricular function has not been described.

Left ventricular contraction via ventricular systolic interaction is considered to play an important role in right ventricular function (Santamore and Gray, Jr. 1996). Therefore the effect of inotropes on the left ventricle may have significant effects on right ventricular function (Santamore and Gray, Jr. 1996; Coddens, Delooft et al. 1993).

1.8 Mixed venous oxygen saturation and one lung anesthesia

1.8.1 Descriptions of P□O_2 during one lung anesthesia

If the Fick equation is solved for C□O_2, then

C□O_2 = CaO_2 – VO_2/CO ..... Equation 1.8.1

Where

C□O_2 is mixed venous oxygen content

CaO_2 is arterial oxygen content

VO_2 is oxygen consumption

CO is cardiac output

If the oxygen dissolved in blood is ignored, and both sides of equation 1.8.1 are divided by hemoglobin concentration [Hb], the following equation can be derived:

S□O_2 = SaO_2 – VO_2/(CO x [Hb] x 1.36) ..... Equation 1.8.2

Where

$S\square O_2$ is venous oxygen saturation

SaO_2 is arterial oxygen saturation and

CO x Hb approximates oxygen delivery to the tissues.

The implications of Equation 1.8.1 are that $C\square O_2$ will increase as CaO_2 increases, provided the relationship of VO_2 to cardiac output remains unchanged. The factors predominantly affecting CaO_2 are oxygen saturation and hemoglobin concentration. Oxygen saturation normally approximates 100%. However, CaO_2 and therefore $C\square O_2$ decrease and increase in parallel with changes in hemoglobin concentration.

As the term on the right hand side of Equation 1.8.1 (the quotient of oxygen consumption and cardiac output) increases, mixed venous oxygenation decreases. The reason is that a greater percentage of oxygen is extracted from the arterial blood. It is not important whether increase in the relationship is due to an increase in oxygen consumption or a decrease in cardiac output. The result is the same. The converse of this relationship also applies.

The implications of equation 1.8.2 are similar to those for equation 1.8.1. The usefulness of Equation 1.8.2 lies therein that in the clinical setting, anesthesiologists commonly measure and are familiar with its components, arterial and venous saturation, hemoglobin concentration and cardiac output. Therefore, the components of equation 1.8.2 are more familiar to clinicians than the equation containing oxygen content.

Only two studies have specifically studied what happens to $P\square O_2$ during one lung anesthesia (Zaune, Knarr et al. 1990; Thys, Cohen et al. 1988). Thys et al, (Thys, Cohen et al. 1988) and Zuane and colleagues (Zaune, Knarr et al. 1990) demonstrated a decrease in $P\square O_2$ and an increase in both oxygen delivery and consumption after initiation of one lung ventilation. The ratio of DO_2 to VO_2 did not change and $P\square O_2$ did not correlate with cardiac output or oxygen consumption. If the relationship of DO_2 to VO_2 is unchanged, we may conclude that the decrease in $P\square O_2$ is attributable to a decrease in the PaO_2.

Various other studies have reported data obtained during one lung anesthesia that include $P\square O_2$ or $S\square O_2$. A full picture of hemodynamics including oxygen flux data is not always given in these studies. This makes their interpretation difficult.

- Malmkvist and colleagues (Malmkvist, Fletcher et al. 1989; Werner, Malmkvist et al. 1984) described a decrease in $P\square O_2$ from 5.1 ± 0.6 kPa before pleurectomy to 4.2 ± 0.6 kPa during one lung anesthesia. They used pethidine (350 to 850 mg) and 50% nitrous oxide for anesthesia. Cardiac index did not change and no further oxygen flux data are available.

- Various studies by Cohen et al, during one lung anesthesia have reported data on $P\square O_2$:
  a. $S\square O_2$ decreased on administration of $PEEP_{10}$ or $PEEP_{10}/CPAP_{10}$ from 83.8 ± 1.4% to 78.6 ± 1.7%. These investigators did not attempt to make an association between $S\square O_2$, hemodynamics and oxygenation (Cohen, Eisenkraft et al. 1988).
  b. $CPAP_{10}$ applied to the non-dependent lung was associated with an increase in $S\square O_2$ from 78 ± 7.5% to 82 ± 6.8% and in PaO_2 from 80 ± 26 mm Hg to 126 ± 59 mm Hg (Cohen, Thys et al.

1985a). During this study, an important observation was made. It was noted that if the tip of the pulmonary artery catheter is located in the collapsed lung, the measured P□O_2 is lower than, and is not a reflection of the true mixed venous saturation (Cohen, Thys et al. 1985a).

c. $PEEP_{10}$ was applied to the dependent lung during isoflurane and 50% nitrous oxide anesthesia. PaO_2 increased whereas no difference in the S□O_2 (77% ± 5) was described on administration of PEEP, despite an associated decrease in cardiac output (Cohen, Thys et al. 1985b).

d. The effect of PEEP in hypoxic patients during one lung anesthesia was studied. Anesthesia was maintained with an unspecified dosage of fentanyl, pancuronium and 1 to 1.5% isoflurane. P□O_2 did not differ between one and two-lung ventilation, nor did it differ between hypoxic and normoxic patients. No oxygen flux data is reported (Cohen and Eisenkraft 1996).

- Mathru and colleagues (Mathru, Dries et al. 1990) studied the effect of cardiac output on gas exchange during one lung anesthesia using enflurane. They described an S□O_2 of 60 ± 6.9% during one lung anesthesia that increased to 74.6 ± 2.8% on administration of dobutamine. Dobutamine administration was also associated with an increase in PaO_2 and DO_2 and a decrease in shunt and $C(a\text{-}v)O_2$. No explanation for the decrease in shunt is given and neither is the influence of P□O_2 on PaO_2 mentioned in the discussion. That increases in P□O_2 may favourably influence PaO_2 during one lung anesthesia is an interesting avenue to explore.

- Pagel et al, (Pagel, Fu et al. 1998) describe a decrease in P□O_2 on initiation of one lung ventilation with desflurane and isoflurane albeit that no change in VO_2 and an increase in cardiac output occurred.

1.8.2 The increase in shunt fraction during one lung ventilation

The shunt fraction has been shown to increase during one lung ventilation to 36% (Cohen, Eisenkraft et al. 1988), 38% (Torda, McCulloch et al. 1974) or 25% (Weinreich, Silvay et al. 1980) at an FiO_2 of 0.5, or 38% (Capan, Turndorf et al. 1980), 39% (Torda, McCulloch et al. 1974) or 36% (Weinreich, Silvay et al. 1980) if an FiO_2 of 1.0 is used to ventilate the dependent lung.

1.8.3 The effect of P□O_2 on arterial oxygen tension in the presence of a shunt

P□O_2 may significantly influence PaO_2 in the presence of a shunt or alveolar hypoxemia as induced by low V/Q units (West 1990; Domino, Borowec et al. 1986; West 1985). In the presence of a decrease in PAO_2, blood entering the capillary is subjected to a low driving pressure of oxygen across the alveolar capillary membrane and therefore the rate of movement of oxygen across the capillary is slower. A significant difference between PAO_2 and PcO_2 may occur under these circumstances. The PAO_2-PcO_2 difference may be further exaggerated when the time that blood spends in the pulmonary capillary is shortened as may happen during exercise or the administration of positive inotropic drugs (West 1990; West 1985) (Figure 1.8.3.1).

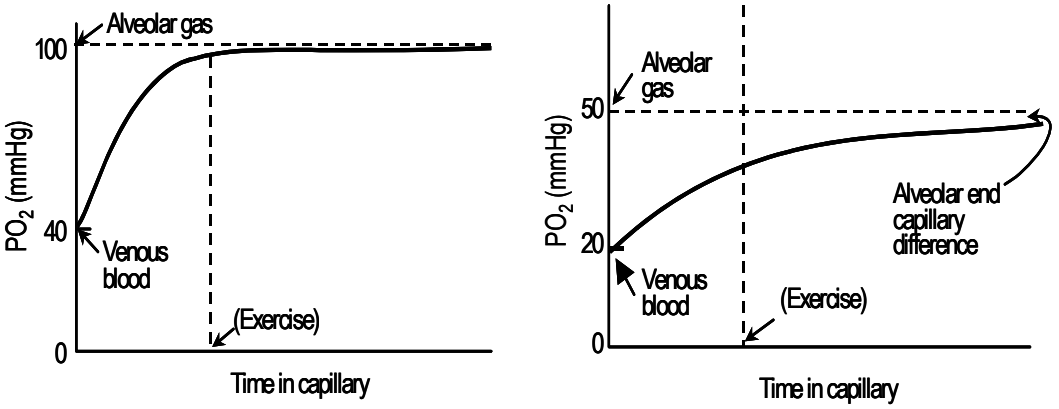


Figure 1.8.3.1 The rise in PO_2 as blood flows along the pulmonary capillary. Blood enters the capillary at a PvO2 of 5.3 kPa. The PO_2 rises rapidly until it approaches the alveolar partial pressure of oxygen. The equilibration is almost complete after a third of the time that the blood spends in the capillary is complete. If the alveolar partial pressure of oxygen is low which reduces the gradient driving blood across the alveolar capillary, the resultant rise in capillary PO2 is slower. There may be a significant difference between the alveolar and capillary partial pressure of oxygen at the end of the capillary. This process will be aggravated by any decrease in the transit time of the blood in the capillary, such as occurs with an increase in cardiac output. Adapted from West, 1985

An increase in cardiac output has been associated with an increase in PaO_2 during one lung anesthesia (Mathru, Dries et al. 1990). On the other hand, if cardiac output decreases due to a rise in right ventricular afterload or the deleterious effects of anesthesia, both P□O_2 and arterial oxygenation will decrease if VO_2 remains unchanged (Domino, Borowec et al. 1986; Mathers, Benumof et al. 1977). Thus, the interaction of cardiac output, P□O_2 in the presence of the large shunt that exists during OLA, has not yet been clarified (Domino, Borowec et al. 1986).

Furthermore, P□O_2 exercises significant influence on the hypoxic pulmonary vasoconstriction response (Benumof 1985). This may have a significant effect on the opposition to pulmonary blood flow in the non-hypoxic ventilated lung (Pease, Benumof et al. 1982).

1.9 Hypothesis

The right ventricle is a thin walled structure that can generate considerably less power than the thicker walled LV. It possesses little reserve to deal with an acute rise in afterload as may occur during acute lung injury or after lung resection (Reed, Spinale et al. 1992). As afterload progressively increases and the pulmonary vascular and right ventricular elastance become equal, the coupling of the RV and its load changes from operating at maximal efficiency to working at maximal SW. Eventually, when pulmonary elastance exceeds RV elastance, the RV makes the transition from pressure to a flow pump and may fail. Thus, the RV may be the limiting factor in the circulation and determine survival of the organism. (Calvin, Jr. 1991) During intrathoracic surgery, it is common to ventilate only one lung while the other lung is operated on. This gives rise to 3 problems:

1. Loss in lung volume

   The usual reduction in FRC during anesthesia is exaggerated in the dependent lung when the patient is positioned in the lateral decubitus position. This can contribute to an increase in PVR especially if PHPT pre-exists.

2. Acute increase in RV afterload

   An increase in PA pressure and PVR may result in an acute increase in RV afterload and impair matching between the RV and its afterload. How exactly the right ventricle performs during OLA has not been well studied.

3. Arterial hypoxia

   Arterial hypoxemia, due mainly to pulmonary shunt, may present a clinical problem during one lung ventilation. The relative resistances of the pulmonary vascular beds of the dependent and non-dependent lungs are an important factor governing arterial oxygenation during one lung anesthesia. A poorly performing right ventricle as a cause of circulatory impairment, may lead to mixed venous desaturation which will contribute significantly to the hypoxemia in the presence of a large shunt (West 1985). Venous desaturation as a cause of hypoxemia during one lung anesthesia has not as yet been systematically addressed in the literature (Cohen 1995; Benumof 1991).

The hypotheses that will be examined, state:

1. RV performance and coupling with its afterload is adversely affected during one lung anesthesia by the increase in pulmonary vascular resistance.
2. The following therapeutic modalities will prove to benefit RV-PA coupling:
   a. Inotropic support will favourably readjust the relationship between right ventricular stroke work and the load faced by the RV. This will improve the ability of the RV to cope with an increase in afterload during OLA.
   b. The application of positive end expiratory pressure (PEEP) to the dependent lung will restore the decrease in lung volume usually seen during OLA. This should reduce indices of RV afterload, minimize RV-afterload mismatch and enhance arterial oxygenation.
3. Furthermore, in the presence of the large shunt that occurs during OLA, mixed venous oxygenation will most likely play an important role in arterial oxygenation. Mixed venous oxygenation reflects the balance of systemic oxygen supply to oxygen demand, which will be affected by RV performance and the factors influencing it. Therefore optimising RV performance and thereby PvO_2 will improve arterial oxygenation during OLA.

2. Methods

2.1 Consent, inclusion and exclusion criteria

Institutional research committee approval was obtained for the study (Research Committee Study 97/028). The ethical standards used conformed to the Declaration of Helsinki[#]. A copy of the patient information and consent form that was used to recruit patients is included in the appendix to this document.

Inclusion criteria to qualify for enrolment in this study were:

- Patients who were scheduled for thoracotomy and pulmonary surgery utilizing one lung anaesthesia,
- The ability to obtain informed consent preoperatively (see informed consent document: section 5.2) and,
- Patients above 18 years of age.

Patients that were excluded from this study were those that:

- Did not qualify for pulmonary surgery according to the criteria used at our institution (Coetzee, 2000),
- In whom there was preoperative evidence of left ventricular pathology (e.g. ischemic heart disease, systemic hypertension, left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or valvular disease),
- Exhibited any clinical evidence of functional hemodynamic disturbances due to acute blood loss, fever, pregnancy, arteriovenous fistulae, heart failure,
- Exhibited biochemical evidence of renal disease (urea > 7 $mmol.l^{-1}$ or creatinine > 150 $umol.l^{-1}$),
- Had hemoglobin concentrations of less than 10 grams per 100 millilitres of blood,
- Were scheduled for lung volume reduction surgery,
- In whom the duration of surgery was expected to be less than 60 minutes and,
- Had a family or personal history of metabolic muscle disease (e.g. malignant hyperthermia, myasthenia gravis or Eaton Lambert syndrome).

2.2 Preoperative assessment of patients

In addition to clinical assessment and chest roentgenology of all the patients, the investigations delineated in the section below were obtained as frequently as was possible, even if not indicated for selection for suitability for lung resection. Brief descriptions of the methods and laboratory quality control protocols are included in this section.

2.2.1 Pulmonary function tests

The pulmonary function tests described in this section were conducted by the clinical technologists of the lung function laboratory of the respiratory unit of the department of internal medicine of the University of Stellenbosch

[#] Recommendations Guiding Medical Physicians in Biomedical Research Involving Human Subjects: Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and most recently amended by the World Medical Assembly in the year 2000 CE (Edinburgh, Scotland). See appendix to this thesis for the most current version of this document.

located at Tygerberg Academic Hospital.

2.2.2 Flow-volume loops

The flow-volume loops were recorded from a wedge spirometer (Med Science Corporation, Model 570, United States of America). Quality control included daily calibration of the spirometer for both volume and flow by the injection of 3 litres of air from a calibrated syringe. Furthermore, three successive maximal effort flow-volume loops were obtained from each subject.

Spirometry was performed with the patient in the sitting position and while wearing a nose clip. A period of quiet breathing was maintained until a similar tidal volume was measured for three consecutive breaths. The subject was then instructed to exhale slowly and maximally from resting, end-expiration to residual volume. Once residual volume was reached, the subject was exhorted to inhale as fast, forcefully and deeply as possible to total lung capacity, then to hold inspiratory effort at total lung capacity for 1-2 seconds, and thereafter to exhale as rapidly, forcefully and completely as possible for at least 6 seconds or until no more gas could be exhaled (Van Schalkwyk, Schultz et al. 2001; Basson 1996). The flow-volume curve with the greatest sum of FEV_1 and FVC was used for analysis (Van Schalkwyk, Schultz et al. 2001; Basson 1996).

The following variables were recorded:

- Forced expiratory vital capacity (FVC), forced expiratory volume in 1.0 second (FEV_1),
- Forced expiratory volume in 1 second expressed as a percentage of the FVC (FEV_1/FVC) and,
- Peak inspiratory flow rate (PIFR), and peak expiratory flow rate (PEFR).

Those variables influenced by height or weight were expressed as a percentage of predicted normal values obtained from the combined regression equations of Schoenberg et al. (Schoenberg, Beck et al. 1978) and Grimby and Soderholm (Grimby and Sonderholm 1967).

2.2.2.1 Lung volumes determined by whole body plethysmography

Lung volumes were measured with a plethysmograph, (Jaeger Masterlab, Erich Jaeger, Wurzburg, Federal Republic of Germany). The principles of the plethysmograph are based on Boyle's law. This law relates pressure to volume.. Boyle's law states that if a given mass of gas is compressed at a constant temperature, the product of pressure (P) and volume (V) is constant (Ruppel 1998; Basson 1996).

$$P_1V_1 = k \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 2.2.2.1.1}$$

Pressure fluctuations result from the compression and decompression of gas within both the subjects' thorax and the body-box. These pressure changes are then related to volume changes by calibration. The calibration is done by measuring pressure changes that occur in response to a known volume of air that is added to the body-box. Measurement of lung volumes is performed with the patient in the sitting position while wearing a nose clip. After explanation of the manoeuvre, tidal breathing was maintained while the plethysmograph was completely sealed off to atmosphere. To measure intrathoracic gas volume, the patient is asked to perform rapid shallow breathing (panting) manoeuvres against a closed shutter with an open glottis.

First consider the gas inside the body-box. The pressure (P_1) and volume (V_1) are known from the prior calibration

manoeuvre. The patient is asked to pant. A pressure transducer monitors pressure changes in the plethysmograph. P_2 represents the pressure after an inspiratory effort and ΔV represents the change in the body-box (or lung) volume. Therefore

$$P_1V_1 = P_2 (V_1-\Delta V) \quad \text{.....} \quad \text{Equation 2.2.2.1.2}$$

Next consider the gas in the thorax. A mouth pressure transducer is coupled to an electronic shutter mechanism. The transducer records mouth pressures when the airway is occluded. It is assumed that mouth pressure reflects alveolar pressure when the shutter blocks the airway. The following relationship then applies to the pressure and volume at the mouth during panting:

$$P_2V_2 = (P_2 + \Delta P)(V_2+ \Delta V) \quad \text{.....} \quad \text{Equation 2.2.2.1.3}$$

Where

P_2	=	alveolar pressure as reflected by mouth pressure
ΔP	=	change in pressure during panting against the shutter
V_2	=	intrathoracic gas volume (FRC)
ΔV	=	change in volume due to compression of the chest by the respiratory muscles when the airway is obstructed.

The final step in determination of lung volumes using the plethysmograph is the performance of a vital capacity manoeuvre. The other lung volumes are then determined mathematically using the following equations:

TLC	= VC + RV	.....	Equation 2.2.2.1.4
VC	= IRV + Vt + ERV	.....	Equation 2.2.2.1.5
FRC (ITGV)	= ERV + RV	.....	Equation 2.2.2.1.6

Where

VC	=	vital capacity
IRV	=	inspiratory reserve volume
ERV	=	expiratory reserve volume
FRC	=	functional residual capacity
TLC	=	total lung capacity
ITGV	=	intrathoracic gas volume.
RV	=	residual volume
Vt	=	tidal volume

ITGV, RV, and TLC were expressed as a percentage of predicted normal values obtained from the combined regression equations of Schoenberg et al. (Schoenberg, Beck et al. 1978) and Grimby and Soderholm (Grimby and Sonderholm 1967).

2.2.2.2 Determination of FRC using helium dilution

FRC was also measured using helium dilution technique (Jaeger Masterlab, Erich Jaeger, Wurzburg, Federal Republic of Germany). This technique measures the volume of the FRC but excludes the volume of gas distal to occluded airways. The volume of gas distal to occluded airways (the intrathoracic gas volume) *is* included in measurements made using plethysmography.

The principles of helium dilution technique are as follows (Ruppel 1998; Basson 1996; West 1985). The subject breathes in helium gas of a known concentration. Helium is nearly insoluble in blood and is therefore not rapidly taken up from the alveoli. After a number of breaths, the helium is diluted equally in both the FRC and the breathing system. The minimal amount of helium that is lost from the system allows FRC to be determined using the principle of conservation of matter. In other words, the amount of helium in the breathing system present before equilibration (the product of concentration and volume or $C_1 \times V_1$) is a known quantity. The same amount of helium is present in the system after equilibration ($C_2 \times (V_1+V_2)$). V_2 is the desired and unknown quantity and represents FRC. C_2 represents the new concentration of helium after dilution with the FRC (V_2) has occurred. C_2 is therefore measured and is therefore used to calculate the unknown variable V_2 (FRC) using the following formula:

$C_1 \times V_1 = (C_2 \times (V_1+V_2))$ ..... Equation 2.2.2.2.1

2.2.2.3 Pulmonary diffusion capacity

Diffusion capacity is the rate of transfer of gas across a membrane at a particular partial pressure gradient across the membrane.

$D_L = V_{GAS} / (P_1-P_2)$ ..... Equation 2.2.2.3.1

Where

D_L = Diffusion capacity for carbon monoxide

V_{GAS} = volume of gas transferred per unit time

P_1 = the partial pressure of the indicator gas proximal to the membrane over which the gas has to diffuse (in this case the partial pressure of carbon monoxide in the alveoli).

P_2 = the partial pressure of the indicator gas distal to the membrane over which the gas has diffused (in this case the partial pressure of carbon monoxide in the pulmonary capillary blood).

In practice, we are concerned with oxygen transfer across the alveolar capillary membrane. However, the measurement of diffusion capacity using oxygen is difficult. Pulmonary diffusion capacity is therefore measured using the single-breath, carbon monoxide diffusion (D_LCO) method introduced by Krogh (Jaeger Masterlab, Erich Jaeger, Wurzburg, Federal Republic of Germany). The advantage of using carbon monoxide is that the size of the carbon monoxide molecule is similar to that of oxygen and therefore their diffusion capacities are similar. Furthermore, as the blood carbon monoxide concentration is *usually* zero, P_2 in equation 2.2.2.3.1 does not have to be measured. The following equation has to be used to calculate diffusing capacity for carbon monoxide:

$D_{L\ CARBON\ MONOXIDE} = V_{CARBON\ MONOXIDE} / (P_{A\ CARBON\ MONOXIDE})$ ..... Equation 2.2.2.3.2

The amount of carbon monoxide transferred across the membrane per minute is calculated using the following principles.

1. Alveolar volume is calculated using helium dilution.
2. The patient exhales to residual volume. They then inhale rapidly to TLC from a reservoir that contains a mixture containing 0.2 to 0.3% carbon monoxide. This breath is held for approximately 10 seconds. The subject then exhales to RV. During this exhalation, a sample of alveolar gas is obtained after the dead space gas has been discarded. The fractional concentration of carbon monoxide is measured in the inhaled gas and exhaled sample.
3. V_{GAS} is calculated as the product of alveolar volume and the difference between the concentration in the alveoli at the start and end of the breathold, divided by the breathold time.

4. D_LCO is expressed as a proportion of the alveolar gas volume. D_LCO is therefore reported in units of millilitres per minute per mm Hg alveolar partial pressure per litre of the FRC.

D_LCO was measured three times for each subject. It was ensured that the inspired volume was within 5% of the inspired vital capacity obtained in the flow-volume loop. To ensure reproducibility, the three D_LCO values had to be within 5% of one another.

2.2.2.4 Exercise testing to determine maximum oxygen consumption

Continuous progressive exercise testing on a treadmill was utilised for the determination of maximum oxygen consumption (VO_2 max).

The treadmill (Trackmaster, ETL testing laboratories, New York, USA) was linked to a computer running a dedicated software program (Cardio$_2$ Combined VO_2 ECG Exercise System, Medical Graphics Corporation, St. Paul, Minnesota, USA). The modified Balke protocol was used. This protocol accommodates individual patient needs by allowing a walking or running speed that is comfortable for the patients. The speed is increased by 1 km/h every minute up to a maximum. After the maximum is attained, speed is kept constant while elevation is increased by 2% every minute. Patients were exhorted to attain at least 85% of their predicted heart rate. Predicted maximum heart rate was determined by using following equation (Basson 1996):

Maximal predicted heart rate = 210 - 0.65 x age ..... Equation 2.2.2.4.1

The exercise study was terminated when either *symptoms* of fatigue, myocardial ischemia, or *signs* suggestive of myocardial ischemia on the 12 lead ECG system or a decrease in blood pressure below the resting value occurred (Basson 1996).

An infrared analyser was used for the analysis of CO_2. A fuel cell oxygen analyser measured mixed expired oxygen concentration. A breath-by-breath system provided gas exchange data for each individual breath. To determine oxygen consumption, the following equation was used:

$VO_2 = (V_I \times F_IO_2) - (V_E \times F_EO_2)$ ..... Equation 2.2.2.4.2

Where	F_IO_2	=	Mixed inspired oxygen concentration
	F_EO2	=	Mixed expired oxygen concentration
	V_E	=	Expired minute volume
	V_I	=	Inspired minute volume
	VO_2	=	Oxygen consumption in milliliters per minute

To determine desaturation during exercise, a pulse oximeter (Ohmeda Biox 3700, Louisville, CO, USA) was attached to an earlobe and stabilized with adhesive tape. The lead connecting the patient sensor to the monitor was affixed to a headband for additional stabilization.

2.2.3 Differential ventilation and perfusion radioisotope scintigram

Pre-operatively, as many of the patients as possible underwent differential ventilation-perfusion lung scanning. This was conducted at the Department of Nuclear Medicine of Tygerberg Academic Hospital and the University of Stellenbosch.

To evaluate lung perfusion, Technetium 99 labelled microspheres were injected intravenously. 95% of the microspheres are removed from the circulation on their first pass through the pulmonary capillary bed (Basson 1996). Ventilation studies are conducted using inhalation of radioactive Krypton 81 gas. The differential distribution of both these isotopes was studied with an Opscon gamma scintillation camera (Searle, Radiographics, Scintiview) connected to a computer. To ensure quality control of the gamma camera, a source of cobalt 67 was counted and imaged daily. Linearity of the system was checked weekly.

2.3 Preparation of patients

2.3.1 Premedication and preoperative sedation

Premedication comprising 0.05 $mg.kg^{-1}$ of lorazepam was administered orally in two divided dosages. The first dose was administered the evening before surgery and the second dose was administered two hours pre-operatively. On arrival in the operating room, additional sedation (up to 2 mg of lorazepam intravenously) was administered if considered necessary by the investigator.

2.3.2 Randomisation

Patients were randomly assigned to either the control or intervention groups. This was done by blind card draw on the morning of surgery.

2.3.3 Temporal description of preoperative preparation, intraoperative management and monitoring of patients in the operating theatre in all groups

While the patient was awake and following the infiltration of local anesthetic (2% lignocaine), a thoracic epidural catheter and the following vascular lines were placed: a peripheral venous cannula, a 20 gauge radial arterial cannula and an internal jugular vein 8.5 French gauge introducer sheath. The sheath was always placed on the same side as the hemithorax that was going to be surgically opened. A balloon tipped thermodilution pulmonary artery catheter (PAC) with either a standard thermistor (response time 1200 milliseconds) (Arrow®, Reading, PA, USA) or a fast response thermistor (response time 95 milliseconds) (REF-1®, Baxter Edwards, Santa Ana, California) was placed via the introducer sheath (Lichtwarck-Aschoff, Leucht et al. 1994; Vincent, Thirion et al. 1986).

Radial and pulmonary arterial pressures were transduced (Medex Medical® MX9504, Rossendale, Lancashire, Great Britain) and displayed continuously on a multichannel monitor (Siemens® Sirecust 1281, Erlangen, Germany or Datex®, Helsinki, Finland). In the supine position, the transducers were zeroed at the level of the midaxillary line. On turning the patient into the lateral decubitus position (LDP), transducers were zeroed at the level of the sternum. A calibration of 100 mmHg was applied to the transducers using the built in calibration feature of the Medex MX9504 transducer. Care was taken to optimise the frequency response of the catheter system by elimination of all air bubbles and blood clots. To further ensure optimal dynamic response of the catheter-transducer system, the proximal lumen of the PAC was connected directly to the pressure transducer without any added connecting tubing.

Cardiac output was measured by thermodilution (REF-1 cardiac output computer, Baxter Edwards, Santa Ana, California). Three measurements of cardiac output were made per step. The average of the three measurements was taken as being the cardiac output for that step. Each measurement was made at the end of expiration. The

indicator for determining cardiac output comprised iced normal saline injected at approximately 4^{O} Celsius. An inline sensor was used to measure the temperature of the injectate. The injectate port of the fast response catheter was positioned in the right atrium 1 cm proximal to the tricuspid valve. This was accomplished by inspection of the pressure waveform transduced from the injectate port of the catheter (Rafferty, Durkin et al. 1993). Mixed venous samples were obtained by withdrawing blood from the distal lumen of the pulmonary artery catheter after it had been withdrawn into the right ventricle. Before and after sampling of mixed venous blood, a right ventricular position of the catheter tip was confirmed by identifying a RV waveform.

Further monitoring included ECG, inspired oxygen partial pressure, pulse oximetry, end tidal isoflurane and carbon dioxide partial pressures (Datex®, Helsinki, Finland), blood temperature and airway pressure. Arterial and venous blood gases, pH, hemoglobin, hematocrit and bicarbonate levels were measured at each step (Nova 1 or Nova 5 blood gas analyser, Massachusetts, USA).

2.4 Induction and maintenance of anesthesia, ventilation and fluid management strategies

Prior to induction of anesthesia, patients were administered up to 7 ml.kg^{-1} of 6% hydroxyethyl starch. The aim of this manoeuvre was to raise the central venous pressure by 2 to 4 mmHg above their baseline value. Thereafter, while the patients breathed 100% oxygen at 8 litres per minute delivered via a facemask attached to a circle-absorber breathing circuit, a computer-controlled alfentanil infusion[2] targeted to achieve and maintain a plasma concentration of 280 ng.ml^{-1} throughout surgery, was commenced. When the patient became apnoeic or unresponsive to verbal stimuli, etomidate 0.1 to 0.3 mg.kg^{-1} was titrated intravenously to further induce unconsciousness. Thereafter, pancuronium 0.1 mg.kg^{-1} was administered intravenously. Manual intermittent positive pressure ventilation with a mask was then commenced. The anesthetic mixture during mask ventilation comprised 100% oxygen at 4 litres per minute and an inspired concentration of 1 kPa isoflurane (Heerdt, Gandhi et al. 1998).

Approximately 5 minutes after commencement of facemask ventilation, endobronchial intubation with an appropriately sized left sided double lumen tube (DLT) was performed (Hannallah, Benumof et al. 1997; Brodsky, Macario et al. 1996; Slinger 1995). The position of the DLT was confirmed clinically (auscultation, chest movement). When the patient was turned into the LDP, the DLT position was confirmed with both auscultation and, when considered necessary, with a flexible fibreoptic bronchoscope (Cohen, Neustein et al. 1995; Brodsky 1994; Benumof 1993; Benumof 1986). A right-sided DLT was only to be used if anatomical or pathophysiological considerations (tumour in left main bronchus, tortuous and narrow left main bronchus) precluded the use of a left sided tube. Intermittent positive pressure ventilation (Ohmeda 7000 anesthesia ventilator, Madison, USA) was continued at a fresh gas flow of 2 litres per minute utilizing 100% oxygen. An inspired partial pressure of 1 kPa of isoflurane was administered until the end of the study. Tidal volume and respiratory rate during both two and one lung anesthesia were 7 ml.kg^{-1} and 12 breaths per minute respectively. Permissive hypercapnia was to be permitted so that arterial

[2] Stelpump version 1.2 (University of Stellenbosch, South Africa), controlling a Baxter Flo-Guard 6201 volumetric infusion pump (Deerfield, IL, USA).

partial pressures of carbon dioxide of up to 8 to 10 kPa were to be allowed.

Patients were then turned into the lateral decubitus position. A forced air warmer (Bair hugger, Augustine Medical, Minnesota, USA) operating at 38^{o} C was sited over the lower half of the patient's body. From the commencement of one lung ventilation in all patients in all groups, oxygen at 2 litres per minute was insufflated via an 8 French gauge catheter down the non-dependent lung lumen of the DLT. Prior to commencement of surgery, 100 ug of preservative free fentanyl diluted in 10 ml of 0.9% saline was injected into the epidural space. No local anesthetic or other drug was administered via the epidural catheter before the termination of the study period.

The goal of intraoperative fluid management was to maintain central venous pressure and pulmonary artery wedge pressure at pre-induction levels. Fluids used were 6% hydroxyethyl starch (mean molecular weight 200 000 Daltons, substitution ratio 0.5) and packed red blood cells to maintain a hematocrit of 30%.

2.5 Differential management of patients in each of the three groups

The exact sequence of events in the control group is indicated in Table 2.5.1. The intervention groups were designated as the "dobutamine" and "PEEP" groups (Table 2.5.2 and Table 2.5.3). Variables were recorded at each of the times depicted in the three tables in this section. The labels that were used to identify each step were shown in the middle column of the tables. Note that the time of commencement of OLA was considered to be only after thoracotomy had been performed, the pleural cavity had been opened and confirmation of NDL collapse was assured. Surgery was not paused during the measurement of hemodynamic data.

Dobutamine was administered by adding 25 mg of dobutamine to a 200 ml bag of 0.9% saline. The infusion rate equivalent to 3, 5 and 7 ug.kg^{-1}.min^{-1} was calculated. A volumetric infusion pump (Infusomat, B Braun, Federal Republic of Germany) was used to administer the dobutamine at the calculated rate.

Extrinsic PEEP was administered by adding a PEEP value (Ambu ®, USA) between the ventilator and the circle system. The level of extensive PEEP was measured on the pressure gauge of the circle breathing system. PEEPi was measured in this study by employing the end expiratory occlusion (EEO) method (Slinger and Hickey 1998; Rossi, Polese et al. 1995; Simbruner 1986). A clamp was applied just before the end of expiration to the connection between the breathing circuit and the DLT and a connection with a manometer was placed between the clamp and the DLT. A minimum period of one second is required for pressure to equalize between lung units with differing time constants; as long as 5 seconds may be needed to complete this process (Yokota, Toriumi et al. 1996; Rossi, Polese et al. 1995). Allowing sufficient time for lung units with differing (slow) time constants to equilibrate provides a measure of PEEPi that reflects the mean amount of intrinsic PEEP present in the system (Rossi, Polese et al. 1995). PEEPi measured using rapid occlusion of the airway by a shutter at the end of expiration has the disadvantage that it predominantly reflects the intrinsic PEEP present in those lung units with fast time constants (Rossi, Polese et al. 1995). Thus, in the current study, at least 5 seconds were allowed to pass before PEEPi was measured. This method of EEO measures the end-expiratory elastic recoil of the respiratory system under static conditions.

Control group		
Description of steps in control group patients	Step label	Conduct of surgery
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake	
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA	No surgery
15 minutes after commencing one lung ventilation	S3: OLA 15 mins	Surgery commences
5 minutes after step 3 data had been recorded	S4: OLA Control 1	Surgery continues
5 minutes after step 4 data had been recorded	S5: OLA Control 2	Surgery continues
5 minutes after step 5 data had been recorded	S6: OLA Control 3	Surgery continues
5 minutes after step 6 data had been recorded	S7: OLA Control 4	Surgery continues

Tables 2.5.1 (above) and 2.5.2 (below) The sequence of events in the control and dobutamine groups respectively.

Dobutamine group		
Description of steps in patients administered dobutamine	Step label	Conduct of surgery
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake	
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA	No surgery
15 minutes after commencing one lung ventilation	S3: OLA 15 mins	Surgery commences
5 minutes after an infusion of dobutamine 3 $ug.kg^{-1}.min^{-1}$ had commenced	S4: Dobutamine 3	Surgery continues
5 minutes after an infusion of dobutamine 5 $ug.kg^{-1}.min^{-1}$ had commenced	S5: Dobutamine 5	Surgery continues
5 minutes after an infusion of dobutamine 7 $ug.kg^{-1}.min^{-1}$ had commenced	S6: Dobutamine 7	Surgery continues

PEEP group		
Description of steps in patients administered PEEP	Step label	Conduct of surgery
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake	
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA	No surgery
15 minutes after commencing one lung ventilation	S3: OLA 15 mins	Surgery commences
10 minutes after $PEEP_5$ was applied to the dependent lung,	S4: $PEEP_5$	Surgery continues
5 minutes after $PEEP_{10}$ was applied to the dependent lung,	S5: $PEEP_{10}$	Surgery continues

Table 2.5.3 The sequence of events in the PEEP group.

2.6 Data collection

Baseline hemodynamic values were recorded once the monitors had been calibrated. Hemodynamic data was collected both on a dedicated form and using a personal computer running "Alab" (Stellenbosch University and Cirrlus Development Systems, South Africa). Electronic data collection consisted of a 30 second recording of ECG, pulmonary arterial, right ventricular and peripheral arterial waveforms. This data was recorded at 100 hertz on "Alab" while intermittent positive pressure ventilation (IPPV) continued.

Values that were recorded included: heart rate, arterial and pulmonary arterial blood pressures, pulmonary artery wedge and central venous pressure, right ventricular pressures at the beginning and end of diastole, peak right ventricular pressure, cardiac output[ψ], right ventricular ejection fraction (RVEF)[ψ], right ventricular end-diastolic volume (RVEDV)[ψ], PA and systemic end systolic pressures (Pes), arterial and mixed venous blood gases, hematocrit, hemoglobin concentration, blood temperature as measured at the distal thermistor of the pulmonary artery catheter, partial pressure of carbon dioxide at the end of expiration, the partial pressure of isoflurane at end of expiration, peak airway pressure, intrinsic and externally applied PEEP, expired tidal volume and respiratory rate. Blood for determination of arterial and venous gases were immediately placed on ice inside the refrigerator in the anteroom of the theatre and analysed within 10 minutes of being collected.

All data collected (demographic data (age, weight, sex, operation, operation side, underlying pathology) as well as the data from the preoperative pulmonary function tests and differential ventilation perfusion scans and the intraoperative data) was transcribed to an Excel® spreadsheet (Microsoft Corporation, USA).

If the surgery terminated before all steps could be performed, the data collected up to that point were to be used.

[ψ] The Baxter cardiac output computer was used to determine cardiac output, right ventricular ejection fraction and right ventricular end-diastolic volume.

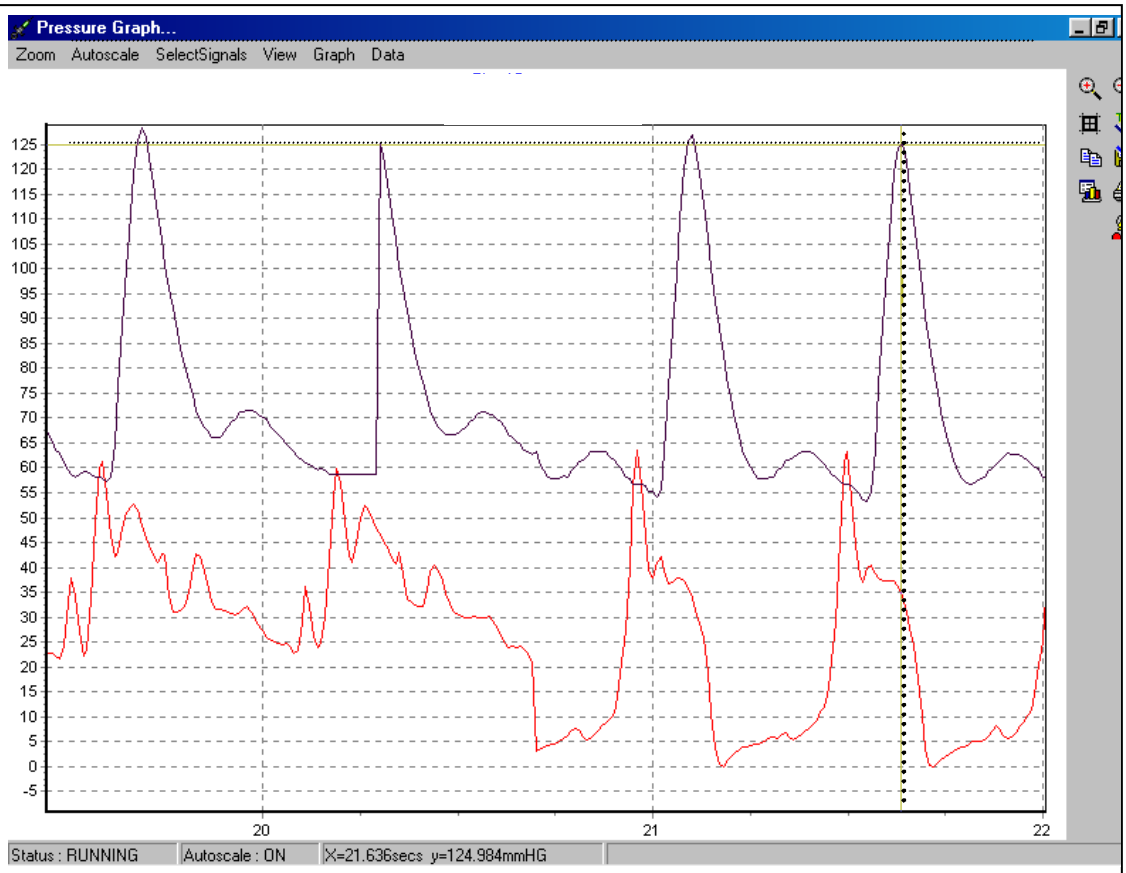


Figure 2.6.1. A "screenshot" of part of a 30 second recording epoch made in "Alab". The "Y" axis represents pressure in mm Hg and the X-axis represents time in seconds. The top tracing is a recording of arterial pressure. The bottom tracing is a recording of pulmonary arterial pressure versus time and then right ventricular pressure versus time. The two middle beats of the 4 represented in the bottom trace occur during changeover of the recording from PA to RV. These beats adjacent to the changeover were not used for measurement of pressure. Note the cursor function in "Alab" used to measure pressures. The crosshairs are moved by using the mouse and the pressure and time values at the crosshairs are indicated in the information bar at the bottom of the screen. For instance, the systolic arterial pressure at the 4th beat of the above window measured at 124.984 mm Hg using the crosshairs. Such values were rounded off to the nearest mm Hg.

2.7 The formulae for derived parameters

	Abbreviation	Units	Formula
Body surface area	BSA	m^2	$(length_{cm}^{0.725})$ $(weight_{kg}^{0.425})$ (0.007184)
Cardiac index	CI	$ml.m^{-2}.minute^{-1}$	CO/BSA
Stroke volume	SV	$ml.beat^{-1}$	CO/HR
Stroke index	SI	$ml.beat^{-1}.m^{-2}$	SV/BSA
Mean arterial pressure	MAP	mm Hg	((Systolic arterial pressure-diastolic arterial pressure)/3) + (diastolic arterial pressure)
Mean pulmonary arterial pressure	mean PAP	mm Hg	((Systolic pulmonary arterial pressure-diastolic pulmonary arterial pressure)/3) + (diastolic pulmonary arterial pressure)
Left ventricular stroke work index	LVSWI	$g.m.m^{-2}$	(MAP – PAWP)(CI/HR) x 0.0136
Right ventricular stroke work index	RVSWI	$g.m.m^{-2}$	(mean PAP – CVP)(CI/HR) x 0.0136
Systemic vascular resistance	SVR	$dynes.secs.cm^{-5}$	(MAP – CVP)/CO
Pulmonary vascular resistance	PVR	$dynes.secs.cm^{-5}$	(PAP-LAP)/CO where PAWP is considered an indication of LAP
Right ventricular coronary perfusion pressure	RV CPP	mm Hg	The difference between mean systemic arterial and mean PA pressure

Table 2.7.1 Derived hemodynamic parameters were calculated using the above formulae (Mark, Slaughter et al. 2000; Reich, Moskowirz et al. 1999).

	Abbreviation	Units	Formula
Dynamic lung compliance		ml.cm H_2O^{-1}	Vt/(Peak airway pressure – $PEEP_{EXTRINSIC}$)
Alveolar oxygen tension	P_AO_2	kPa	(Pb – PH_2O)-(P_aCO_2/RQ)
Arterial oxygen content	CaO_2	ml.100ml^{-1}	([Hb] x SaO_2 x 1.39)+(PaO_2 x 0.0031)
Mixed venous oxygen content	C□O_2	ml.100ml^{-1}	([Hb] x S□O_2 x 1.39)+(P□O_2 x 0.0031)
Pulmonary capillary oxygen content	CcO_2	ml.100ml^{-1}	([Hb] x ScO_2 x 1.39)+(PcO_2 x 0.0031)
Intrapulmonary shunt	Qs/Qt	%	(CcO_2-CaO_2)/(CcO_2-C□O_2)

Table 2.7.2 Respiratory parameters were calculated using the following formulae (Moon and Camporesi 2000; Reich, Moskowirz et al. 1999; Costarino and Marshall 1995).

	Abbreviation	Units	Formula
Oxygen delivery	DO_2	ml.$minute^{-1}$	CO x CaO_2 x 10
Oxygen delivery index	DO_2I	ml.$minute^{-1}.m^{-2}$	DO_2/BSA
Oxygen consumption	VO_2	ml.$minute^{-1}$	CO(CaO_2-C□O_2)
Oxygen consumption index	VO_2I	ml.$minute^{-1}.m^{-2}$	VO_2/BSA
Oxygen extraction ratio	OER	Ratio	(CaO_2-C□O_2)/CaO_2

Table 2.7.4 Formulae were used to determine parameters of oxygen delivery and consumption (Reich, Moskowirz et al. 1999).

	Abbreviation	Units	Formula
Aortic elastance	Ea aorta	mm Hg.ml^{-1}	Aortic Pes/SV or MAP/SV
Pulmonary arterial elastance	Ea PA	mm Hg.ml^{-1}	PA Pes/SV or mean PAP/SV
PA characteristic impedance	Rc PA	dynes.secs.cm^{-5}	See section 2.9 below and/or Rc = Rp – (Ea/total cardiac cycle time)
Total pulmonary vascular resistance	R_{TOTAL} PA	dynes.secs.cm^{-5}	Method 1: Calculated using the sum of PVR and Ro. Rc is determined as in section 2.9. It is assumed that PVR approximates Rp. Method 2: R_{TOTAL} = Ea PA . total cardiac cycle time. (Sagawa, Maughan et al. 1988. Page 238. See also Equation 1.4.4.12) Total cardiac cycle time was physically measured from the recordings made in "Alab".
Pulmonary arterial compliance	PA compliance	ml.cm H_2O^{-1}	Calculated using the formula, Compliance = Tau/$R_{TOTAL,}$ where "tau" is the diastolic time constant of the pulmonary vasculature. R_{TOTAL} can be determined by using either of the methods described above.

Table 2.7.3 Parameters of the Windkessel model were calculated using the above formulae (Tanaka, Oshita et al. 1998; Senzaki, Chen et al. 1996; Fourie, Coetzee et al. 1992b; Dahlgren, Veintemilla et al. 1991; Sagawa, Maughan et al. 1988: Cardiac contraction and the pressure volume loop. Chapter 5, page 238). As there was ringing in the PA catheter-transducer system, using Pes was not considered to be an accurate representation of PA end-systolic pressure. Tanaka, Oshita et al. 1998, Senzaki, Chen et al. 1996 and Sagawa, Maughan et al. 1988 consider that Pes and mean arterial and pulmonary arterial pressures approximate each other. Therefore, mean PAP was used to calculate PA elastance in this study. Note that the formula for Rc = Rp – (Ea/total cardiac cycle time) is derived from Sagawa, Maughan et al. 1988.

In the above formulae the following assumptions were considered reasonable:

1. For the determination of the alveolar partial pressure of oxygen:
   a. That P_B was 101.3 kPa

b. That P_{H_2O} was 6.2 kPa

c. That the respiratory quotient (RQ) was 0.8

2. To determine the amount of oxygen in pulmonary capillary blood, the following assumptions were considered reasonable:

a. That the partial pressure of oxygen in the pulmonary capillary (PcO_2) was equal to P_AO_2,

b. That the hemoglobin of pulmonary capillary blood (ScO_2) is fully saturated with oxygen and,

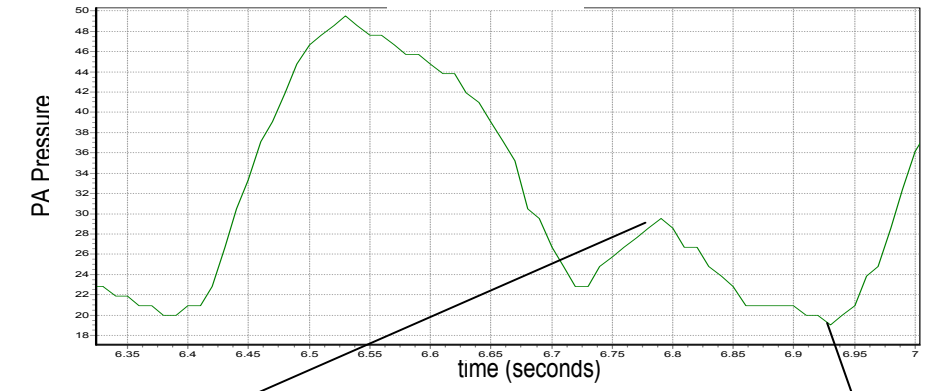
c. The pulmonary capillary hemoglobin concentration was equal to that of the arterial hemoglobin concentration.

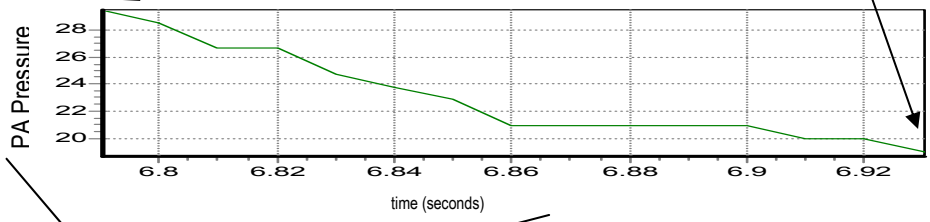
3. In the above formulae, the partial pressure of oxygen used to calculate dissolved oxygen content is measured in mmHg. One kPa equals 7.55 mmHg.

2.8 Reasons to terminate the study

Reasons for removing patients and their associated data from the study:

- Inability to separate the lungs because of an inability to correctly place, or subsequent malposition of, the double lumen tube,
- Failure to adhere to the study protocol because of clinical necessity and,
- Massive hemorrhage (defined for the purposes of this study to be greater than 500 ml of blood loss over a period of 10 minutes).





PAP mm Hg	Time seconds	ln PAP
28.57	0	3.352357
26.67	0.01	3.283539
26.67	0.02	3.283539
24.76	0.03	3.209229
23.81	0.04	3.170106
22.86	0.05	3.129389
20.95	0.06	3.042139
20.95	0.07	3.042139
20.95	0.08	3.042139
20.95	0.09	3.042139
20.95	0.1	3.042139
20	0.11	2.995732
20	0.12	2.995732
19.05	0.13	2.947067
20	0.11	2.995732
20	0.12	2.995732
19.05	0.13	2.947067

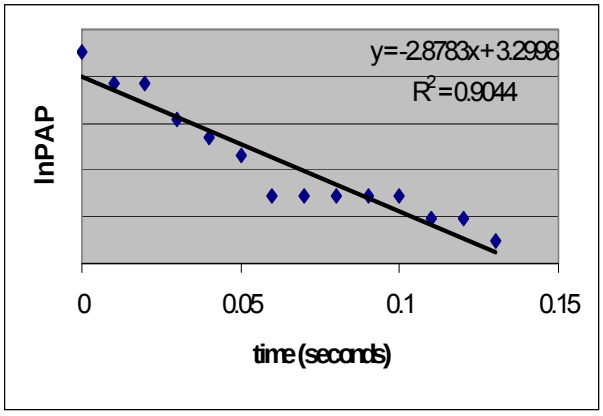


Figure 2.9.1.1. The method of obtaining the time constant of the pulmonary circulation. The exponential decline of the pressure curve during diastole is selected and typically, 15 to 35 data points are imported into the spreadsheet. The inverse of the absolute value of the slope of the semi logarithmic plot is the time constant.

2.9 Derivation of a method for calculating characteristic impedance (Rc)#

Ea may be calculated from the following two formulae with good agreement between the two (Sagawa, Maughan et al. 1988: Cardiac contraction and the pressure volume loop. Chapter 5, page 239; Fourie, Coetzee 1992, Figures 1.4.4.2 and 1.4.4.3):

$$Ea = R_{total} / (ts + \tau(1 - e^{-td/\tau})) \quad \text{..... Equation 2.9.1}$$

$$Ea = Pes/SV \quad \text{..... Equation 2.9.2}$$

From Windkessel models of the pulmonary circulation, R_{TOTAL} is comprised of the sum of Rc and Rp. Therefore

$$Ea = (Rc + Rp) / (ts + \tau(1 - e^{-td/\tau})) \quad \text{..... Equation 2.9.3}$$

Solving for Rc

$$(Rc + Rp) = Ea / [(ts + \tau(1 - e^{-td/\tau})]$$

$$Rc = \frac{Pes}{SV\ ((ts + \tau(1 - e^{-td/\tau}))} - Rp \quad \text{..... Equation 2.9.4}$$

Where the units of equation 2.9.4 are:

Resistance:	mmHg.seconds.ml^{-1} (1 mmHg.second.ml^{-1} equals 79.9 dynes.seconds.cm^{-5})
Pes:	mmHg
SV:	ml
ts and td:	seconds
τ:	seconds
$e^{-td/\tau}$:	no units

If it is assumed that Rp ≡ PVR, the parameter τ is required to calculate a value for Rc. τ may be derived from the exponential decline in PA pressure after closure of the pulmonary valve (Fourie, Coetzee et al. 1992b; Westerhof and Elzinga 1991; Laskey, Parker et al. 1990). Thus

$$PAPt = PAPo\ e^{-t/\tau} \quad \text{..... Equation 2.9.5}$$

Where PAPt = pulmonary artery pressure at time t

PAPo = pulmonary artery pressure at the beginning of the function

Taking natural logarithms on both sides of the equation:

Note that the author developed this particular method of deriving characteristic impedance. The method was mathematically verified by Dr Toit Mouton of the department of applied engineering of the University of Stellenbosch. Subsequent to this, a number of articles (Westerhof and Elzinga, 1991; Yin, Liu et al. 1987) using similar methods of deriving characteristic impedance (albeit in the systemic circulation) were discovered using a Medline search. Note also that PVR and Rp are both used to describe pulmonary vascular resistance.

$$LnPAPt = -t/\tau + lnPAPo \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 2.9.6}$$

The data points of the exponential decline in pulmonary artery pressure after closure of the pulmonary valve (pressure and the corresponding time points) were inputted into an Excel® spreadsheet (Figure 2.9.1.1). The natural logarithm of the pressure points were calculated, a semi-logarithmic plot of lnP(t) versus time constructed and a regression in the form of equation 2.9.6 was calculated. The inverse of the absolute value of the slope of the semi-logarithmic plot is the time constant. This method was applied to 5 beats per epoch. The average of these 5 determinations of tau were used to solve for Rc in equation 2.9.3.

2.10 Determination of the frequency response of the transducer-catheter systems

The flush method as described by Gardner and employed by Schwid was used to determine the natural frequency and damping coefficient of the arterial and pulmonary arterial catheter and transducer systems (Schwid 1988). The high-pressure flush valve was opened and then rapidly released with the catheters still connected to the patient. This has shown to provide reliable testing of the transducer, connecting tubing and the intravascular catheter (Schwid 1988). The tracing was recorded using "Alab". To ensure accuracy of the measurements, the tracing was amplified in Alab. This results in the problem that the "paper speed" is not known. The natural frequency response is given by the inverse of the wavelength in millimetres as illustrated in Figure 2.10.1 (Mark, Slaughter et al. 2000; Sykes, Vickers et al. 1994; Schwid 1988; Foster and Roelofse 1987; Fourie, Badenhorst et al. 1987). The damping coefficient was determined by measuring the amplitude ratio of subsequent oscillations (A1 and A2) after the flush had been terminated. This ratio was then related to the table 2.10.1 to determine the damping coefficient of the system (Foster and Roelofse 1987; Gardner 1981). These measurements were conducted for both systemic and pulmonary arterial transducer systems.

Amplitude Ratio A_1/A_2	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.05	0.02
Damping coefficient	0	0.03	0.07	0.11	0.16	0.22	0.28	0.36	0.46	0.6	0.7	0.9

Table 2.10.1 A table relating amplitude ratios and damping coefficients. Reproduced from "Databook of anaesthesia and critical care", Foster and Roelofse, Springer-Verlag, Berlin, 1987

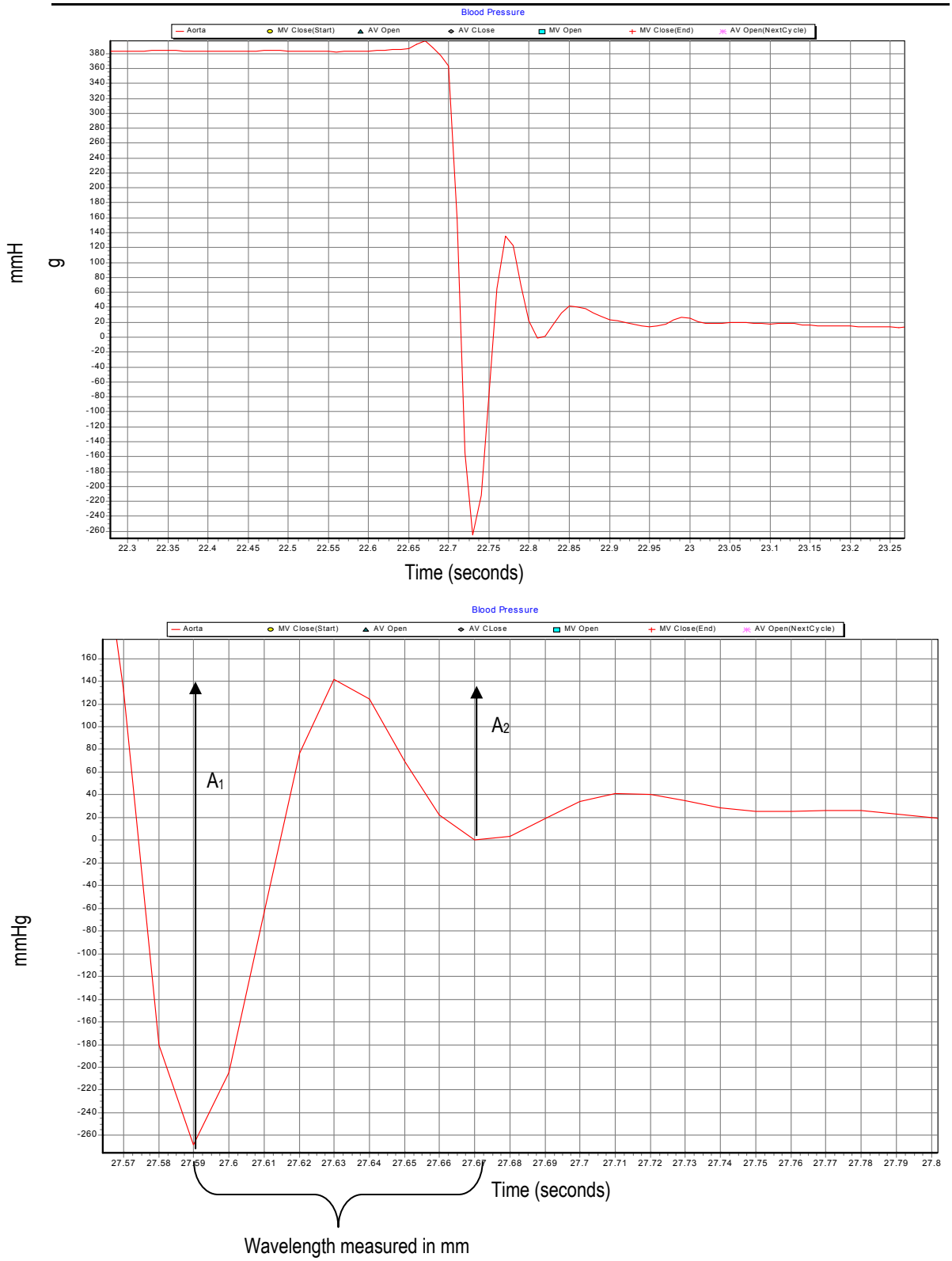


Figure 2.10.1 *A diagram illustrating the principles of determination of frequency response of an arterial system. The traces have been imported from Alab and expanded to allow accurate measurements to be made. The natural frequency response is given by the inverse of the wavelength in millimetres. The damping coefficient was determined by measuring the amplitude ratio of subsequent oscillations (A_1 and A_2) after the flush had been terminated. This ratio was then related to Table 2.10.1 to determine the damping coefficient of the system.*

2.11 Models used to study right ventricular performance

The following models of right ventricular performance and afterload during OLA will be studied:

- The components of the Windkessel model of the pulmonary circulation (Ro, Rp and C) will be calculated.
- The coupling of the RV to its load: i.e. indices of right ventricular performance e.g. RVSWI, RVEF, SV related to indices of afterload (PVR, PA Ea, PAP, pulmonary vascular Rc and compliance).
- Indices of right ventricular preload (RVEDV and RVEDP).
- Pulmonary and systemic hemodynamics and oxygen flux data, including P□O_2 will be studied.
- The influence of P□O_2 on arterial oxygenation in the presence of the shunt that exists during OLA will be studied.

2.12 Statistical analysis

Statistical analysis was performed in collaboration with Professor J.F. Coetzee of the Department of Anesthesiology and Critical Care, University of Stellenbosch. The sample size that would be needed was calculated before commencement of the study. For the purposes of the calculation of sample size, it was decided that a 20% change in cardiac output would represent a clinically significant change. Using this value, it was estimated that that five patients per group would be needed for the study to have a power of 80% to detect a 5% difference between the various steps.

The data collected was inputted into an Excel® spreadsheet and each data point was checked before analysis. Sigmastat for Windows® version 2.03 (SPSS Incorporated, San Rafael, California) was used to perform statistical analysis.

Data was tested for normality of distribution (Kolmogorov Smirnov test; $p < 0.05$) and equality of variance (Levene Median test; $p < 0.05$)

Analysis of whether differences existed between different epochs within a particular group was performed using analysis of variance (ANOVA) for repeated measures (RM). Between groups analyses for the first three steps of the 3 different groups was conducted using one way ANOVA. If differences existed, these were identified using multiple comparisons were made (Student-Newman-Keuls test). Analysis of whether differences existed between the first three steps of the groups was done using one-way ANOVA. An alpha value equal to or less than 0.05 was regarded as indicating a significant difference.

Nominal and ordinal data were compared using the Chi-squared test. The strength of associations was measured using the Pearson product moment correlation for data that was normally distributed and exhibited a constant variance. For data that was not normally distributed and/or did not exhibit constant variance, Spearman rank order correlation was used to measure the strength of associations.

3. Results

3.1 Demographics

Group	Patient	Operation	Pathology
Control	Ca	Left pneumonectomy	Destroyed lung for completion pneumonectomy, large bullous right upper lobe
Control	Cb	Right lower lobe lobectomy	Carcinoma bronchus, COPD, smoker
Control	Cc	Left upper lobe lobectomy	Left upper lobe mass
Control	Cd	Left lower lobe lobectomy	Pulmonary tuberculosis, hemoptysis
Control	Ce	Left pneumonectomy	Pulmonary tuberculosis, destroyed left lung
Control	Cf	Right upper lobe lobectomy	Mass of unknown etiology
Control	Cg	Right pneumonectomy	Empyema, previous lobectomy
Control	Ch	Left upper lobe lobectomy	Pulmonary tuberculosis, mycetoma
Control	Ci	Right upper lobe lobectomy	Carcinoma bronchus
Control	Cj	Left pneumonectomy	Giant bullous, COPD
Control	Ck	Right pneumonectomy	Carcinoma bronchus
Control	Cl	Left upper lobe cystectomy	Echinococcus cyst
Control	Cm	Left upper lobe lobectomy	Carcinoma bronchus
Control	Cn	Right upper lobe lobectomy	Pulmonary tuberculosis, mycetoma
Control	Co	Right upper lobe lobectomy	Bullous lung disease
Control	Cp	Left upper lobe lobectomy	Carcinoma bronchus
Control	Cq	Right pneumonectomy	Pulmonary tuberculosis, aspergilloma
Control	Cr	Left pleurectomy	Spontaneous pneumothorax, COPD
Control	Cs	Right pneumonectomy	Pulmonary tuberculosis, destroyed lung
Control	Ct	Left upper lobe lobectomy	Pulmonary tuberculosis, hemoptysis

Group	Patient	Operation	Pathology
Control	Cu	Right pleurectomy	Spontaneous pneumothorax, COPD
Control	Cv	Right pneumonectomy	Pulmonary tuberculosis, hemoptysis
Control	Cw	Left lower lobe lobectomy	Carcinoma bronchus
Control	Cx	Right upper lobe lobectomy	Pulmonary tuberculosis, mycetoma
Control	Cy	Left pneumonectomy	Carcinoma bronchus
Control	Cz	Right upper lobe lobectomy	Pulmonary tuberculosis
Dobutamine	Da	Left pneumonectomy	Pulmonary tuberculosis
Dobutamine	Db	Right pneumonectomy	Carcinoma bronchus
Dobutamine	Dc	Right pleurectomy	Pulmonary tuberculosis
Dobutamine	Dd	Diaphragmatic plication	Normal lung parenchyma
Dobutamine	De	Left pneumonectomy	Tumour left main bronchus
Dobutamine	Df	Right pneumonectomy	Post tuberculosis destroyed lung
Dobutamine	Dg	Right pneumonectomy	Cystic fibrosis
Dobutamine	Dh	Right upper lobe lobectomy	Right upper lobe bullous
Dobutamine	Di	Left upper lobe bullectomy	COPD, bullous lung disease
Dobutamine	Dj	Left upper lobe lobectomy	Pulmonary tuberculosis, mycetoma
Dobutamine	Dk	Right upper lobe wedge resection	Tumour unknown origin
Dobutamine	Dl	Right pneumonectomy	Post tuberculous bronchiectasis, hemoptysis
Dobutamine	Dm	Right pneumonectomy	Bullous disease
Dobutamine	Dn	Left pneumonectomy	Post tuberculosis destroyed lung
Dobutamine	Do	Right pneumonectomy	Undifferentiated carcinoma bronchus
Dobutamine	Dp	Left lower lobe lobectomy	Bronchiectasis
Dobutamine	Dq	Right upper lobe bullectomy	Bullous lung disease
Dobutamine	Dr	Right cystectomy	Very large echinococcus cyst

Group	Patient	Operation	Pathology
Dobutamine	Ds	Right upper lobe lobectomy	Tumour of unknown origin, COPD, pulmonary tuberculosis
Dobutamine	Dt	Right pneumonectomy	Post tuberculous bronchiectasis
Dobutamine	Du	Left pneumonectomy	Post tuberculous destroyed lung
Dobutamine	Dv	Right pneumonectomy	Destroyed right lung, hemoptysis
Dobutamine	Dw	Right upper lobe lobectomy	Previous pulmonary tuberculosis, hemoptysis
Dobutamine	Dx	Right upper lobe wedge resection	Tumour of unknown origin for frozen section
PEEP	Pa	Left upper lobe lobectomy	Unknown pathology
PEEP	Pb	Right pneumonectomy	Carcinoma bronchus
PEEP	Pc	Right pleurectomy	Pulmonary tuberculosis, fibrosis in other lung
PEEP	Pd	Right pneumonectomy	Post tuberculous lung destruction
PEEP	Pe	Right lower lobe lobectomy	Carcinoma bronchus
PEEP	Pf	Left upper lobe lobectomy	Pulmonary tuberculosis, mycetoma
PEEP	Pg	Right pneumonectomy	Post tuberculous bronchiectasis and hemoptysis
PEEP	Ph	Left pneumonectomy	Post tuberculous lung destruction
PEEP	Pi	Left lower lobe lobectomy	Bronchiectasis, cause unknown
PEEP	Pj	Left segmentectomy	Tumour, possibly lymphoma
PEEP	Pk	Right upper lobe bullectomy	COPD, bullous lung disease

Table 3.1.1 A list of the diagnoses and operations performed. Male subjects comprised 55.5%, 54% and 64% respectively for the control, dobutamine and PEEP groups. Post tuberculous disease was present in 45% of the patients and 40% of subjects had chronic obstructive pulmonary disease and/or carcinoma of the bronchus.

Table 3.1.2 *(On following page)* The demographics of the 3 groups. Data is presented as the mean (standard deviation) for each parameter. No differences were found between the groups.

Demographics							
		Control		Dobutamine		PEEP	
	Units	□	SD.	□	SD.	□	SD.
Age	Years	47.6	14.5	40.8	13.7	45.6	16.1
Weight	Kg	59.8	12.1	59.4	18.3	63.8	15.0
Length	m	162	8	164	10	170	10
Body surface area	m^2	1.63	0.2	1.63	0.3	1.73	0.2
Forced vital capacity	% predicted	95	26	80	26	92	24
Forced expiratory volume in one second	% predicted	83	23	69	22	76	24
FEV_1/FVC	% predicted	74	14	76	14	69	8.5
Peak expiratory flow rate	% predicted	89	24.5	84	27	89	26
Peak inspiratory flow rate	% predicted	68	16	61	25	67	20
Intrathoracic gas volume (plethysmography)	% predicted	151	66	138	46	168	57
Residual volume (plethysmography)	% predicted	123	50	146	42	194	74
RV (Helium dilution)	% predicted	98	40	107	38	107.5	45
TLC (Helium dilution)	% predicted	119	40	104	27	106	32.5
D_LCO/Va	% predicted	76	25	81	24	80	12
VO_{2MAX}	$ml.kg^{-1}.min^{-1}$	17	4	20	5	20	4
Oxyhemoglobin saturation on exercise	%	93	4	89	5.5	89	9
Preoperative ventilation to right lung	% total	52	20.5	50.5	23	47	26
Preoperative ventilation to left lung	% total	47.5	20	49	22	53	26
Preoperative perfusion to left lung	% total	47	24	52	28	64	25
Preoperative perfusion to right lung	% total	52.5	24	45	30	36	25
Perfusion to lung to be collapsed (i.e. NDL)	% total	36	19	25.5	16.5	33	21
New York Heart Association Dyspnoea		2	1	2	1	2	1.6

3.2 Between group comparisons

Between groups comparison of the variables recorded during the first 3 steps (i.e. while the patients were awake, subjected to 2 and one lung anesthesia in the LDP) was done. The only difference between the groups was that body temperature was lower in the PEEP than the dobutamine group when the patients awake (Table 3.2.1). This difference did not persist once the patients were anesthetised. The 0.8 ^{O}C difference in temperature was an isolated finding and is not regarded as a clinically significant difference for the purposes of this study. .

Temperature ^{O}C		
Measured while subjects were awake	□	SD.
Control group	36.7	0.6
Dobutamine group ##	37.0	0.5
PEEP group ##	36.2	0.7

Table 3.2.1 Between group analyses of first three steps revealed that the only difference was that temperature differed while the patients were awake. ## PEEP and dobutamine groups differ, p = 0.035.

3.3 Within group comparisons (Tabulated)

Explanatory note to the tables in section 3.3

Each group's data is presented in a separate set of tables (control group is presented in section 3.3.1, dobutamine group in section 3.3.2 and PEEP group in section 3.3.3). Each results table contains within it two separate sets of tables.

1. The data table:
   - i. The top two rows of the data table identify which parameters data is contained in the table.
   - ii. The steps are identified on the left of the table.
   - iii. Each parameter spans three columns:
     - a. The number of patients in which a particular parameter was observed is noted in the column marked "n",
     - b. The arithmetic mean is noted by the column marked "□",
     - c. The column marked "SD" notes the standard deviation.
2. The "intragroup differences" tables: Repeated measures analysis of variance was employed to do within group comparisons of individual parameters. Any differences that existed were analysed using the Student-Newman-Keuls post hoc test. The intragroup differences that were identified are noted in tabular

form in the tables with solid black table headings situated below the data table. The p values for each difference are included in this table.

3.3.1 Control group tables

Control group						
	Expired tidal volume ($ml.kg^{-1}$)			Expired minute volume (litres)		
	n	□	SD.	n	□	SD.
S1: Awake	-	-	-	-	-	-
S2: Two-lung Anesthesia, LDP	16	7.8	2.1	16	4.8	1.3
S3: After 15 minutes of OLA	17	6.7	2.2	17	4.2	1.2
S4: OLA, Control step 1	18	6.7	2.0	18	4.3	0.8
S5: OLA, Control step 2	16	6.7	1.7	16	4.2	0.9
S6: OLA, Control step 3	11	6.1	1.9	11	4.4	0.9
S7: OLA, Control step 4	5	6.2	1.4	5	4.2	0.7

Table 3.3.1.1

No changes in expired tidal volume or minute volume occurred on initiation of OLA. No further changes tidal volume or expired minute volume occurred as OLA progressed.

Control group			
	End tidal isoflurane partial pressure (kPa)		
	n	□	SD.
S1: Awake	-	-	-
S2: Two-lung Anesthesia, LDP	11	0.4	0.2
S3: After 15 minutes of OLA	12	0.5	0.2
S4: OLA, Control step 1	12	0.5	0.1
S5: OLA, Control step 2	10	0.4	0.2
S6: OLA, Control step 3	9	0.5	0.2
S7: OLA, Control step 4	4	0.5	0.2

Table 3.3.1.2

No differences in the end tidal partial pressure of isoflurane occurred between any of the steps in the control group.

Control group									
	Peak airway pressure (cm H_20)			Dynamic compliance (ml.cm H_20^{-1})			Intrinsic PEEP (cm H_20)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	-	-	-	-	-	-	-	-	-
S2: Two-lung Anesthesia, LDP	16	21	6.6	16	24	9.5	7	3	2.5
S3: After 15 minutes of OLA	17	27	8.2	17	15	5.1	11	3	2.7
S4: OLA, Control step 1	18	28	6.8	18	15	5.4	10	3	2.7
S5: OLA, Control step 2	16	28	7.8	16	15	5.6	8	5	3.1
S6: OLA, Control step 3	11	27	7.6	11	15	4.9	8	3	1.6
S7: OLA, Control step 4	5	25	5.5	5	16	5.6	4	3	2.6

Peak airway pressure	p
S2 < S3	0.05
S2 < S4	0.003
S2 < S5	0.003
S2 < S6	0.008

Dynamic compliance	p
S2 > S3	<0.001
S2 > S4	<0.001
S2 > S5	<0.001
S2 > S6	<0.001
S2 > S7	<0.001

Table 3.3.1.3

Peak airway pressure increased and dynamic compliance decreased on initiation of OLA compared to when two-lungs were being ventilated. These changes in peak airway pressure and dynamic compliance were sustained as OLA progressed in the control group. The amount of intrinsic PEEP present did not differ between two-lung and OLA, or change as OLA progressed.

Control group															
	$PaCO_2$ (kPa)			$PeCO_2$ (kPa)			pH arterial			HCO_3 (mmol.litre^{-1})			BE (mmol.litre^{-1})		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	20	5.0	0.6				20	7.42	0.02	20	21	2.9	20	1.7	2.5
S2: Two-lung Anesthesia, LDP	16	5.7	1.1	16	4.6	0.5	16	7.36	0.05	16	26	2.1	16	0.0	1.5
S3: After 15 minutes of OLA	17	6.0	1.7	17	5.3	1.1	17	7.34	0.06	17	26	1.5	17	-0.8	1.4
S4: OLA, Control step 1	18	6.2	1.4	18	5.4	1.0	18	7.33	0.06	18	26	2.9	18	-1.2	2.4
S5: OLA, Control step 2	15	6.5	1.8	16	5.7	1.2	15	7.31	0.08	15	26	2.5	15	-1.1	2.1
S6: OLA, Control step 3	9	6.3	0.7	11	5.9	1.2	9	7.31	0.04	9	26	1.8	9	-1.6	2.1
S7: OLA, Control step 4	5	6.9	1.1	5	6.0	1.0	5	7.30	0.08	5	27	1.5	5	-0.2	2.6

$PaCO_2$	p
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001
S1 < S7	<0.001
S2 < S5	0.03
S2 < S7.	0.032

$PeCO_2$	p
S2 < S3	<0.001
S2 < S4	0.001
S2 < S5	<0.001
S2 < S6	<0.001
S2 < S7	<0.001

pH arterial	p
S1 > S2	0.007
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	<0.001
S2 vs. S3	0.053
S2 > S4	0.002
S2 > S5	<0.001
S2 > S6	0.004
S2 > S7	0.003

BE	p
S1 > S2	0.015
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	0.002
S2 > S4	0.002
S2 > S5	0.002
S2 > S6	0.024

Table 3.3.1.4

Arterial carbon dioxide tension increased during the first OLA control step (S4) compared to when the patients were awake (S1). Arterial carbon dioxide tensions continued to exceed awake levels during the rest of the OLA control steps. During OLA control steps 5 and 7, arterial carbon dioxide tensions also exceeded those observed during two-lung anesthesia.

During all OLA steps, expired carbon dioxide tensions exceeded those seen during two-lung anesthesia. Arterial pH was

also lower during all the OLA control steps (S4 to S7) than when two-lungs were being ventilated. No intragroup differences in bicarbonate concentrations were observed in the control group. When the patients were awake, base excess exceeded that measured during all other steps in the control group. Base excess was also lower during all the OLA control steps (S4 to S7) compared with the two-lung anesthesia step.

Control group												
	PaO_2 (kPa)			SaO_2 (%)			P□O_2 (kPa)			S□O_2 (%)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	20	11.2	1.9	20	96.3	2.4	20	5.5	0.5	20	74.9	5.5
S2: Two-lung Anesthesia, LDP	16	58.9	8.8	16	99.9	0.04	16	9.3	1.4	16	91.8	2.3
S3: After 15 minutes of OLA	17	38.4	17.3	17	99.1	2.1	17	8.5	1.8	17	88.4	5.1
S4: OLA, Control step 1	18	34.8	15.4	18	99.1	2.4	18	8.3	1.6	18	87.5	4.8
S5: OLA, Control step 2	15	35.4	13.3	15	99.1	2.7	15	8.3	1.9	15	86.8	5.2
S6: OLA, Control step 3	9	36.9	14.2	9	99.4	1.2	9	8.8	2.9	9	86.8	6.3
S7: OLA, Control step 4	5	32.5	10.3	5	99.6	0.6	5	8.1	0.8	5	86.8	1.6

PaO_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S2 > S3	<0.001
S2 > S4	<0.001
S2 > S5	<0.001
S2 > S6	<0.001
S2 > S7	<0.001

SaO_2	p
S1 < S2	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	0.047
S1 < S7	0.006

P□O_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S6	<0.001
S1 < S7	<0.001

S□O_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S2 > S6	0.011

Table 3.3.1.5

During two-lung anesthesia, the PaO_2 exceeded that seen during all other steps in the control group. During the first 3 steps of OLA (S3,4,5), PaO_2 also exceeded that seen when the patients were awake. However, during the last two OLA control steps (S6 and S7), PaO_2 was not statistically different from those seen during the awake state. Arterial oxygen saturation was less during the awake state than during steps S2,4,5,6 and 7 in the control group.

Mixed venous oxygen tension and mixed venous oxygen saturation increased by 70% and 23% respectively after induction of anesthesia compared with when the patients were awake. Similar increases in the venous oxygen tension and saturation were sustained during steps 3, 6, and 7 of OLA. During two-lung anesthesia, S□O_2 also exceeded that measured during OLA control group step 3.

Control group						
	CaO_2 (ml.100ml^{-1})			C□O_2 (ml.100ml^{-1})		
	n	□	SD.	n	□	SD.
S1: Awake	20	17.84	2.2	20	13.81	2.0
S2: Two-lung Anesthesia, LDP	16	17.07	2.1	16	14.69	2.1
S3: After 15 minutes of OLA	17	16.17	2.5	17	13.89	2.4
S4: OLA, Control step 1	18	16.20	2.4	18	13.82	2.3
S5: OLA, Control step 2	15	16.23	2.2	15	13.72	2.2
S6: OLA, Control step 3	9	16.18	1.8	9	13.60	1.9
S7: OLA, Control step 4	5	17.25	3.3	5	14.58	2.8

CaO_2	p
S2 < S1	0.043
S3 < S1	0.010
S4 < S1	0.003
S5 < S1	0.012
S6 < S1	<0.001

Table 3.3.1.6

CaO_2 was higher when the patients were awake than in steps 2,3,4,5 and 7. No intragroup differences in mixed venous oxygen content occurred.

Control group									
	Shunt Qs/Qt (%)			$D(A\text{-}a)O_2$ (kPa)			PaO_2/FiO_2		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	18	17.3	8.4	18	7.7	1.9	18	53.1	9.2
S2: Two-lung Anesthesia, LDP	14	26.0	8.6	14	36.3	9.3	14	58.6	9.3
S3: After 15 minutes of OLA	15	36.3	11.8	15	54.2	17.0	15	40.8	17.0
S4: OLA, Control step 1	16	37.1	10.8	16	58.6	15.6	16	36.3	15.5
S5: OLA, Control step 2	14	36.5	8.3	14	59.1	13.6	14	35.8	13.6
S6: OLA, Control step 3	8	35.8	13.2	8	55.0	11.5	8	40.0	11.5
S7: OLA, Control step 4	5	35.6	6.6	5	62.5	10.3	5	32.5	10.3

Shunt Qs/Qt	p
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001
S1 < S7	<0.001
S2 < S4	<0.001
S2 < S5	<0.001
S2 < S6	0.002
S2 vs. S7	0.054

PaO_2/FiO_2	p
S1 > S3	0.016
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	0.001
S1 > S7	0.008
S2 > S3	<0.001
S2 > S4	<0.001
S2 > S5	<0.001
S2 > S6	<0.001
S2 > S7	<0.001

$D(A\text{-}a)O_2$	p
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001
S1 < S7	<0.001
S2 < S4	<0.001
S2 < S5	<0.001
S2 < S6	<0.001
S2 < S7	<0.001

Table 3.3.1.7

The shunt fraction was greater during OLA steps 4,5 and 6 than during the first two steps in the control group. However, during step 7, the shunt did not differ statistically from that calculated for step 2. No progressive increase in the shunt fraction occurred as OLA progressed. The cost of oxygenation, as indicated by the so-called non-invasive indicator of shunt, the $D(A\text{-}a)O_2$ and the ratio of PaO_2/FiO_2, was greater during OLA compared with the awake and two-lung anesthesia steps.

Control group												
	MAP (mmHg)			Systemic Pes (mmHg)			SAP (mmHg)			DAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	19	100	16	19	99	20	19	149	26	19	76	12
S2: Two-lung Anesthesia, LDP	15	79	17	15	79	17	15	112	25	15	64	14
S3: After 15 minutes of OLA	16	88	14	16	84	123	16	125	23	16	69	10
S4: OLA, Control step 1	17	79	20	17	76	20	17	113	32	17	62	15
S5: OLA, Control step 2	15	77	17	15	75	17	15	109	25	15	61	13
S6: OLA, Control step 3	10	81	15	10	77	17	10	115	22	10	64	12
S7: OLA, Control step 4	5	69	17	5	67	19	5	98	27	5	54	12

MAP	p	Systemic Pes	p	SAP	p	DAP	p
S1 > S2	<0.001	S1 > S2	<0.001	S1 > S2	<0.001	S1 > S2	0.003
S1 > S3	0.002	S1 > S3	<0.001	S1 > S3	<0.001	S1 > S3	0.019
S1 > S4	<0.001	S1 > S4	<0.001	S1 > S4	<0.001	S1 > S4	0.002
S1 > S5	<0.001	S1 > S5	<0.001	S1 > S5	<0.001	S1 > S5	0.002
S1 > S6	<0.001	S1 > S6	<0.001	S1 > S6	<0.001	S1 > S6	0.007
S1 > S7	<0.001	S1 > S7	<0.001	S1 > S7	<0.001	S1 > S7	0.004

Table 3.3.1.8

Systolic, diastolic, mean and end systolic systemic arterial pressures were higher when the patients were awake then during all other control group steps.

Control group									
	PAP (mean) (mmHg)			SPAP (mmHg)			DPAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	19	19	5.1	19	33	6.7	19	12	4.9
S2: Two-lung Anesthesia, LDP	15	21	5.9	15	34	9.7	15	14	4.3
S3: After 15 minutes of OLA	16	24	7.7	16	40	12.1	16	16	6.0
S4: OLA, Control step 1	17	22	5.3	17	37	9.4	17	15	5.0
S5: OLA, Control step 2	15	23	6.1	15	37	10.3	15	16	4.6
S6: OLA, Control step 3	10	21	4.3	10	34	6.9	10	14	3.5
S7: OLA, Control step 4	5	25	4.8	5	39	6.2	5	17	4.6

PAP (mean)	p
S1 < S3	0.001
S1 < S5	0.007
S1 < S6	0.04
S1 < S7	0.002
S2 < S3	0.050
S2 < S5	0.004
S2 < S7	0.006

Table 3.3.1.9

Mean pulmonary arterial pressure did not change from when the patients were awake to when 2 lungs were being ventilated in the LDP. However, during all OLA steps except for step 4, mean pulmonary artery pressure exceeded that measured when the patients were awake. Mean pulmonary arterial pressure during OLA in steps 3, 5 and 7 also exceeded that seen when two-lungs were being ventilated. Mean PAP in S3 escaped being statistically different from S2.

Neither PA systolic nor diastolic pulmonary arterial pressures differed between the various steps in the control group.

Control group									
	Cardiac index (litres.min^{-1}.m^{-2})			Stroke index (ml.m^{-2})			Heart rate (beats.min^{-1})		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	20	3.6	0.7	10	44	15	19	82	17
S2: Two-lung Anesthesia, LDP	16	3.4	0.9	15	39	7	15	83	19
S3: After 15 minutes of OLA	17	4.4	1.1	5	43	10	16	98	16
S4: OLA, Control step 1	18	4.0	1.0	17	41	9	17	97	18
S5: OLA, Control step 2	16	4.2	1.6	15	42	11	15	94	16
S6: OLA, Control step 3	11	4.1	1.9	19	41	12	10	93	19
S7: OLA, Control step 4	5	3.6	1.2	16	40	10	5	93	13

Cardiac index	p
S1 < S3	0.02
S2 < S3	0.001
S2 < S4	0.01
S2 < S5	0.006
S2 < S6	0.05

Heart rate	p
S1 < S3	0.001
S1 < S4	0.01
S1 < S5	0.04
S1 < S6	0.01
S2 < S5	0.03
S2 < S6	0.01

Table 3.3.1.10

Cardiac index did not change from when the patients were awake to after induction of anesthesia while two-lungs were being ventilated awake. However, cardiac index did rise on initiation of OLA when compared with both the two-lung anesthesia and awake steps. This increase in cardiac index was sustained until all but the very last step of OLA (S7) at which point cardiac index returned to baseline awake values.

No intragroup changes in stroke index occurred. During steps 4, 5 and 6, heart rate was higher than when the patients were awake. During steps 5 and 6, heart rate was also greater than when two-lungs were being ventilated.

Control group												
	CVP (mmHg)			RVEDP (mmHg)			RVEDVI (ml.m^{-2})			PAWP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	20	5.1	3.2	6	4.8	3.5	4	97	28	20	8.7	4.7
S2: Two-lung Anesthesia, LDP	16	6.7	3.5	6	8.7	4.7	10	111	35	16	10.4	4.1
S3: After 15 minutes of OLA	17	6.5	4.8	6	9.2	3.9	9	106	37	17	11.4	4.9
S4: OLA, Control step 1	18	6.0	3.2	4	7.3	2.9	12	114	32	18	10.3	4.6
S5: OLA, Control step 2	16	6.2	3.6	5	9.2	2.9	13	117	30	16	11.3	4.3
S6: OLA, Control step 3	11	6.2	3.9	2	14.0	1.4	11	117	24	11	9.6	3.8
S7: OLA, Control step 4	5	8.0	2.7	1	13.0	0	12	114	32	5	11.6	3.7

Table 3.3.1.11

No intragroup changes in the indices of right or left ventricular preload occurred.

Control group															
	Ea PA (mmHg.ml^{-1})			PVR (dynes.secs.cm^{-5})			Rc PA[3] (dynes.secs.cm^{-5})			Rc PA[4] (dynes.secs.cm^{-5})			R_{TOTAL} (dynes.secs.cm^{-5})		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	25	0.28	0.1	25	160	77	11	78	99	13	108	93	13	201	74
S2: Two-lung Anesthesia, LDP	21	0.32	0.1	21	156	78	10	64	53	11	92	55	11	200	51
S3: After 15 minutes of OLA	22	0.33	0.03	22	131	59	11	61	53	12	90	63	12	189	58
S4: OLA, Control step 1	24	0.33	0.03	24	153	77	11	70	78	10	92	121	12	207	83
S5: OLA, Control step 2	19	0.35	0.03	19	149	70	9	78	39	9	106	102	9	219	76
S6: OLA, Control step 3	11	0.33	0.03	11	151	40	8	79	99	9	118	132	8	232	86
S7: OLA, Control step 4	6	0.38	0.04	6	173	26	5	43	49	5	67	80	5	194	64

Ea PA	p
S4 > S1	0.035
S5 > S1	0.039
S6 > S1	0.015
S7 > S1	0.001
S7 > S2	0.007
S7 > S3	0.020

Table 3.3.2.12

PA elastance was greater during OLA control steps 4, 5 6 and 7 compared to when patients were awake. In the last OLA control step (S7), PA elastance also exceeded that seen during both two-lung anesthesia (S2) and the first OLA step (S3). No intragroup changes were observed in any of the other indices of pulmonary vascular resistance or impedance.

3. Calculated using Ro as derived using the Windkessel equation

4. Calculated using Ea = R_{TOTAL}/time of the beat

Control group									
	Compliance PA[5] (ml.mmHg^{-1})			Compliance PA[6] (ml.mmHg^{-1})			Tau PA (secs)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	13	2.5	1.0	13	2.2	1.00	9	0.40	0.25
S2: Two-lung Anesthesia, LDP	11	3.8	3.0	11	3.3	2.7	11	0.51	0.45
S3: After 15 minutes of OLA	12	3.1	2.1	12	2.8	2.0	11	0.45	0.30
S4: OLA, Control step 1	10	2.2	1.0	10	2.0	1.0	12	0.41	0.21
S5: OLA, Control step 2	9	2.3	1.8	9	2.3	1.8	10	0.51	0.40
S6: OLA, Control step 3	5	3.3	2.1	5	2.9	2.00	8	0.43	0.16
S7: OLA, Control step 4	5	2.7	1.4	5	2.4	1.3	4	0.39	0.21

Table 3.3.1.13

No intragroup changes in PA compliance or the time constant of the pulmonary circulation were observed.

5. Calculated using Ro as derived using the Windkessel equation

6. Calculated using Rt/time of the beat

Control group						
	SVR (dynes.secs.cm^{-5})			Ea aorta (mmHg.ml^{-1})		
	n	□	SD.	n	□	SD.
S1: Awake	10	1104	515	24	1.5	0.2
S2: Two-lung Anesthesia, LDP	15	1002	483	20	1.2	0.2
S3: After 15 minutes of OLA	5	951	640	22	1.2	0.4
S4: OLA, Control step 1	17	993	445	23	1.2	0.5
S5: OLA, Control step 2	15	1126	315	19	1.5	0.5
S6: OLA, Control step 3	19	1392	351	11	1.2	0.6
S7: OLA, Control step 4	16	993	276	6	1.1	0.6

SVR	p
S1 > S2	0.019
S1 > S3	<0.001
S1 > S4	<0.001
S1 < S5	<0.001
S1 < S6	0.005
S1 > S7	0.015

Table 3.3.1.14

Systemic vascular resistance was less during steps 2,3,4 and 7 than when the patients were awake. However, during steps 5 and 6, systemic vascular resistance exceeded the SVR when the patients were awake.

Aortic elastance did not change from when the patients were awake to the last OLA control step.

Control group									
	RVSWI ($g.m.m^{-2}$)			LVSWI ($g.m.m^{-2}$)			RVEF (%)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	9.29	5.0	10	54.6	10.6	11	35.5	6.2
S2: Two-lung Anesthesia, LDP	15	7.36	2.48	15	36.3	15.3	12	35.8	7.1
S3: After 15 minutes of OLA	5	10.8	4.32	5	43.1	15.6	10	35.9	6.6
S4: OLA, Control step 1	17	9.96	4.79	17	37.0	15.8	12	38.9	7.9
S5: OLA, Control step 2	15	10.6	5.36	15	33.1	15.5	13	36.2	8.5
S6: OLA, Control step 3	19	9.48	4.44	19	35.1	15.7	9	38.7	3.7
S7: OLA, Control step 4	16	10.73	5.69	16	31.3	6.1	4	36.8	1.7

LVSWI	p
S1 > S2	<0.001
S1 > S3	0.006
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	<0.001

Table 3.3.1.15

No intragroup changes in either RVSWI or RVEF were observed in the control group.

Left ventricular stroke work index decreased by 33% on induction of anesthesia compared with the awake state. Throughout OLA, LVSWI remained lower relative to the awake step.

Control group												
	VO_2 index ($ml.min^{-1}.m^{-2}$)			DO_2 index ($ml.min^{-1}.m^{-2}$)			HKT (%)			Temperature (^oC)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	20	141	28	20	641	149	20	39.4	4.7	20	36.7	0.6
S2: Two-lung Anesthesia, LDP	16	78	13	16	582	155	16	34.0	4.5	16	35.8	0.6
S3: After 15 minutes of OLA	17	98	26	17	695	183	17	33.3	4.8	17	35.8	0.5
S4: OLA, Control step 1	18	93	26	18	643	169	18	33.5	4.5	18	35.7	0.5
S5: OLA, Control step 2	15	94	23	15	615	157	15	33.6	4.6	15	35.6	0.5
S6: OLA, Control step 3	9	88	29	9	586	168	9	33.3	4.2	9	35.8	0.6
S7: OLA, Control step 4	5	96	33	5	623	232	5	35.8	7.0	5	35.6	0.8

VO_2 index	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	<0.001

DO_2 index	p
S2 <. S3	0.020

HKT	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1> S5	<0.001
S1> S6	<0.001
S1> S7	0.003

Temperature	p
S1> S2	<0.001
S1> S3	<0.001
S1> S4	<0.001
S1> S5	<0.001
S1> S6	<0.001
S1> S7	<0.001

Table 3.3.1.16

Oxygen consumption decreased by 45% after induction of anesthesia compared with when the patients were awake. During the OLA steps, oxygen consumption was also less (on average 34%) than when the patients were awake.

The only intragroup difference in oxygen delivery was a lower DO_2 during the step when two-lungs were being ventilated (S2) compared with when OLA and surgery commenced (S3).

Both hematocrit and temperature decreased after induction of anesthesia compared with when the patients were awake. No further changes in hematocrit and temperature occurred as OLA progressed.

Control group						
	$CaO_2 - C\square O_2$ (ml.100ml^{-1})			OER		
	n	□	SD.	n	□	SD.
S1: Awake	20	4.0	1.0	18	0.23	0.05
S2: Two-lung Anesthesia, LDP	16	2.4	0.45	14	0.14	0.03
S3: After 15 minutes of OLA	17	2.3	0.45	15	0.14	0.03
S4: OLA, Control step 1	18	2.4	0.52	16	0.15	0.03
S5: OLA, Control step 2	15	2.5	0.47	14	0.16	0.03
S6: OLA, Control step 3	9	2.6	0.95	8	0.16	0.06
S7: OLA, Control step 4	5	2.7	0.47	5	0.16	0.01

$CaO_2 - C\square O_2$	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	<0.001

OER	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S1 > S7	<0.001

Table 3.3.1.17

The arterial-venous oxygen content difference and the oxygen extraction ratio both decreased by 40% after induction of anesthesia compared with when the patients were awake. These decreases in the arterial-venous oxygen content difference and the oxygen extraction ratio were sustained throughout OLA.

3.3.2 Dobutamine group tables

Dobutamine group						
	Tidal volume expired ($ml.kg^{-1}$)			Minute volume expired (litres)		
	n	□	SD.	n	□	SD.
S1: Awake				-	-	-
S2: Two-lung Anesthesia	24	7.1	1.8	24	4.7	1.6
S3: One Lung Anesthesia	23	6.7	2.1	23	4.8	1.3
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	18	5.9	1.4	18	4.4	1.4
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	16	6.5	2.2	15	4.3	1.4
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	15	5.8	1.4	15	4.5	1.3

Table 3.3.2.1

No changes in expired tidal volume or minute volume occurred on initiation of OLA. No further changes in tidal volume or expired minute volume occurred while any of the 3 dosages of dobutamine were being administered.

Dobutamine group									
	Peak airway pressure (cmH_20)			Dynamic compliance ($ml.cmH_20^{-1}$)			Intrinsic PEEP ($cm\ H_20$)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	-	-	-	-	-	-	-	-	-
S2: Two-lung Anesthesia	24	22	7	24	21	8	0	-	-
S3: One Lung Anesthesia	24	26	6	24	15	4	2	3	3
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	26	5	18	14	4	2	4	4
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	29	5	16	13	5	2	5	6
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	27	6	15	12	4	1	9	0

Peak airway pressure	p	Dynamic compliance	p
S2 < S3	<0.001	S2 > S3	<0.001
S2 < S4	<0.001	S2 > S4	<0.001
S2 < S5	<0.001	S2 > S5	<0.001
S2 < S6	<0.001	S2 > S6	<0.001

Table 3.3.2.2

Peak airway pressure increased while dynamic compliance decreased on induction of OLA. These changes were sustained during the OLA steps while dobutamine was being administered.

Intrinsic PEEP was present during all the OLA steps; however, no intragroup differences were observed.

Dobutamine group			
	End tidal isoflurane concentration (kPa)		
	n	□	SD.
S1: Awake	-	-	-
S2: Two-lung Anesthesia	7	0.4	0.2
S3: One Lung Anesthesia	7	0.5	0.2
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	6	0.4	0.2
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	7	0.4	0.2
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	4	0.5	0.1

Table 3.3.2.3

No differences end tidal isoflurane partial pressures between the various steps in the dobutamine group occurred.

Dobutamine group															
	$PaCO_2$ (kPa)			$PeCO_2$ (kPa)			pH arterial			HCO_3 (mmol.litre^{-1})			BE (mmol.litre^{-1})		
	n	□	SD.	n	□	SD.	N	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	5.3	0.7	-	-	-	24	7.43	0.02	24	27.7	2.7	24	2.7	2.0
S2: Two-lung Anesthesia	23	5.8	1.0	24	4.8	1.0	23	7.38	0.05	23	27.3	2.7	23	1.1	2.0
S3: One Lung Anesthesia	23	6.0	0.9	24	5.1	1.1	23	7.35	0.09	23	27.1	2.5	23	0.7	2.2
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	6.7	1.2	18	5.6	1.1	18	7.32	0.06	18	27.2	2.7	18	-0.3	2.4
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	6.9	1.3	16	5.7	1.3	16	7.31	0.07	16	27.5	3.2	16	-0.3	2.9
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	6.5	1.1	15	5.7	1.1	15	7.30	0.07	15	26.3	3.8	15	-1.3	3.7

$PaCO_2$	p
S1 < S2.	0.006
S1 < S3	0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001
S2 < S4	0.022
S2 < S5.	0.009
S2 < S6	0.024
S3 vs. S4	0.065
S3 < S5	0.034
S3 < S6	0.042

$PeCO_2$	p
S2 < S4	0.005
S2 < S5	0.001
S2 < S6	<0.001
S6 < S3	0.02

pH arterial	p
S1 > S2	0.002
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S2 > S5	0.007
S2 > S6	0.008

BE	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S2 > S4	0.004
S2 > S5	0.003
S2 > S6	<0.001
S3 > S4	0.018
S3 > S5	0.023
S3 > S6	<0.001

Table 3.3.2.4

Arterial carbon dioxide tensions increased after induction of anesthesia, and increased progressively as OLA continued. During all dobutamine administration steps, the expired carbon dioxide tensions exceeded those seen during two-lung anesthesia. During the administration of 7μg per kg of dobutamine (S6), $PeCO_2$ also exceeded that seen during OLA when no intervention was applied (S3).

Arterial pH was less during all steps in the dobutamine group compared with when the patients were awake. When dobutamine 5 and 7 μg per kg were administered, arterial pH was less than during the two-lung anesthesia step.

No differences in bicarbonate concentrations were seen between any of the steps in the dobutamine group. Base excess was greater in the awake state relative to all the other steps in the dobutamine group. Base excess was also greater in steps 2 and 3 compared with steps 4,5 and 6.

Dobutamine group												
	PaO_2 (kPa)			SaO_2 (%)			P□O_2 (kPa)			S□O_2 (%)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	11.2	1.9	24	96.0	3.1	24	5.4	0.5	24	75.1	5.7
S2: Two-lung Anesthesia	23	53.4	13.5	23	99.9	0.1	23	8.6	1.7	23	89.9	4.7
S3: One Lung Anesthesia	23	45.4	17.7	23	99.7	0.6	23	9.0	1.7	23	90.6	4.7
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	37.9	19.3	18	98.8	2.6	18	9.0	2.1	18	89.0	5.5
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	38.1	19.6	16	98.5	4.2	16	8.5	2.2	16	85.5	11.9
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	37.7	15.9	15	99.3	1.9	15	9.3	1.6	15	89.9	5.8

PaO_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001
S2 > S3	0.013
S2 > S4	<0.001
S2 > S5	<0.001
S2 > S6	0.001

SaO_2	p
S1 < S2.	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001

PvO_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001

SvO_2	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S1 < S6	<0.001

Table 3.3.2.5

Arterial oxygen tensions and saturations were greater than awake values during all steps after induction of anesthesia. While both lungs were being ventilated, arterial oxygen tension also exceeded that measured both during the OLA steps and when the patients were awake.

Immediately after induction of anesthesia, venous oxygen tension and saturation increased by 60 and 20% respectively relative to the awake values. These increases in venous oxygen tension and saturation were sustained at similar levels during OLA both with and without dobutamine administration.

Dobutamine group						
	CaO_2 ($ml.100ml^{-1}$)			$C\square O_2$ ($ml.100ml^{-1}$)		
	n	□	SD.	n	□	SD.
S1: Awake	24	18.35	2.19	24	14.27	1.91
S2: Two-lung Anesthesia	23	17.98	2.28	23	15.28	2.18
S3: One Lung Anesthesia	23	17.54	3.00	23	15.21	2.86
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	18	17.35	2.97	18	15.12	3.15
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	16	16.49	2.21	16	13.70	2.43
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	15	16.35	2.62	15	14.29	2.60

CaO_2	p
S1 > S5	0.013
S1 > S6	0.013

Table 3.3.2.6

No intragroup differences in mixed venous oxygen content occurred. However, arterial oxygen content was decreased during the dobutamine 5 and 7 $ug.kg^{-1}.min^{-1}$ steps relative to when the patients were awake.

Dobutamine group									
	Shunt Qs/Qt %			$D(A\text{-}a)O_2$ kPa			PaO_2/FiO_2		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	23	18.0	11.2	24	7.7	2	24	53.1	9
S2: Two-lung Anesthesia	23	26.2	7.2	23	41.7	14	23	53.3	13
S3: One Lung Anesthesia	23	32.5	8.3	23	49.6	18	23	45.3	17
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	18	38.5	13.9	18	57.2	19	18	37.8	19
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	16	34.2	7.8	16	56.9	20	16	38.0	19
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	15	39.6	7.5	15	57.3	16	15	37.7	15

Shunt Qs/Qt	p	$D(A\text{-}a)O_2$	p	PaO_2/FiO_2	p
S1 < S2	0.003	S2 > S1	<0.001	S1 > S3	0.021
S1 < S3	<0.001	S3 > S1	<0.001	S1 > S4	0.002
S1 < S4	<0.001	S4 > S1	<0.001	S1 > S5	0.003
S1 < S5	<0.001	S5 > S1	<0.001	S1 > S6	0.003
S1 < S6	<0.001	S6 > S1	<0.001	S2 > S3	0.039
S2 < S3	0.012	S3 > S2	0.013	S2 > S4	0.003
S2 < S4	<0.001	S4 > S2	<0.001	S2 > S5	0.001
S2 < S5	0.010	S5 > S2	<0.001	S2 > S6	0.004
S2 < S6	<0.001	S6 > S2	0.001		

Table 3.3.2.7

The shunt fraction increased by 46% while two-lungs were being ventilated compared with that seen when the patients were awake. A further 24% increase in shunt fraction was noted on institution of OLA (S3) relative to the shunt seen during two-lung anesthesia. Compared with the two-lung anesthesia step, this increase in shunt fraction was sustained during all steps (S4, 5 and 6) during which dobutamine was administered. The increase in $D(A\text{-}a)O_2$ during step 2 indicated an increased cost of arterial oxygenation compared with the awake state. The $D(A\text{-}a)O_2$ increased further during OLA (S3) compared with both the awake and two-lung anesthesia steps. The PaO_2/FiO_2 ratio also indicated that the cost of arterial oxygenation increased after institution of OLA compared with the first two steps; this difference was sustained in the rest of the control group steps.

Dobutamine group												
	MAP (mmHg)			Systemic Pes (mmHg)			SAP (mmHg)			DAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	25	95	13	25	95	14	25	136	18	25	75	12
S2: Two-lung Anesthesia	24	70	16	24	70	15	24	96	19	24	57	14
S3: One Lung Anesthesia	24	84	19	24	81	16	24	116	24	24	68	16
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	84	20	18	79	19	18	121	30	18	65	16
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	88	19	16	82	20	16	127	28	16	68	16
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	88	17	15	81	20	15	133	27	15	64	14

MAP	p
S1 > S2	<0.001
S1 > S3	0.030
S1 vs. S4	0.056
S2 < S3	<0.001
S2 < S4	0.003
S2 < S5	0.001
S2 < S6	0.001

Systemic Pes	p
S1 > S2	<0.001
S1 > S3	0.006
S1 > S4	0.016
S1 > S5	0.019
S1 > S6	0.014
S2 < S3	0.026
S2 < S5	0.039

DAP	p
S2 < S1	<0.001
S2 < S3	0.008
S2 < S4	0.022
S2 < S5	0.024
S2 < S6	0.018

SAP	p
S1 < S2	<0.001
S1 < S3	0.002
S1 < S4	0.039
S2 < S3	<0.001
S2 < S4	<0.001
S2 < S5	<0.001
S2 < S6	<0.001
S6 vs. S3	0.061

Table 3.3.2.8

After induction of anesthesia and while two-lungs were being ventilated (S2), an approximately 27% decrease in both MAP and systemic Pes occurred compared with awake values. During two-lung anesthesia, MAP was also lower than that measured during all the other steps in the dobutamine group. Pes was lower during two-lung anesthesia than in steps 3 and 5. After initiation of OLA (S3), MAP was only 12% less than the when the patients were awake. However, on administration of dobutamine, the MAP was not different from when the patients were awake.

SAP and DAP decreased during two-lung anesthesia compared with all other steps. SAP was also less than baseline awake during OLA (S3) and when dobutamine 3 ug.kg^{-1}.min^{-1} was administered. However, during administration of dobutamine (both 5 and 7 ug.kg^{-1}.min^{-1}), any difference from baseline was no longer apparent.

Dobutamine group									
	PAP (mean) (mmHg)			SPAP (mmHg)			DPAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	25	19	5	25	32	8	25	12	5
S2: Two-lung Anesthesia	24	19	5	24	31	7	24	13	4
S3: One Lung Anesthesia	24	22	6	24	35	10	24	15	6
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	23	6	18	40	10	18	15	5
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	25	7	16	42	12	16	16	5
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	25	6	15	43	12	15	16	5

PAP (mean)	p
S5 > S1	0.002
S5 > S2	0.013
S6 > S1	0.002
S6 > S2	0.014

SPAP	p
S6 > S1	<0.001
S6 > S2	<0.001
S6 > S3	0.042
S5 > S1	<0.001
S5 > S2	<0.001
S5 > S3	0.031
S4 > S1	0.038
S4 > S2	0.024

Table 3.3.2.9

Compared with when the patients were awake, no differences in PA pressures occurred after induction of either two or one lung anesthesia (S2 and S3). The two higher dosages of dobutamine increased mean pulmonary arterial pressure above those seen both while the patient was awake and when both lungs were being ventilated.

No intragroup changes in diastolic PAP were observed in the dobutamine group.

As the dosage of dobutamine was being increased, systolic pulmonary arterial pressure rose progressively.

Dobutamine group									
	Cardiac index (litres.min^{-1}.m^{-2})			Stroke index (ml.min^{-1}.m^{-2})			Heart rate (beats.min^{-1})		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	3.6	0.8	24	46	11	25	85	25
S2: Two-lung Anesthesia	24	3.4	0.9	24	41	12	24	82	13
S3: One Lung Anesthesia	23	4.4	1.1	23	45	15	24	94	14
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	5.2	1.1	18	52	12	18	103	21
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	4.9	1.2	16	46	11	16	108	21
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	5.5	1.2	15	47	12	15	114	23

Cardiac index	P
S6 > S1	<0.001
S6 > S2	<0.001
S6 > S3	<0.001
S6 > S5	0.054
S5 > S1	<0.001
S5 > S2	<0.001
S5 > S3	0.0012
S4 > S1	<0.001
S4 > S2	<0.001
S4 > S3	0.008
S3 > S1	<0.001
S3 > S2	<0.001

Stroke index	P
S2 < S4	0.017

Heart rate	P
S6 > S1	<0.001
S6 > S2	<0.001
S6 > S3	0.002
S5 > S1	<0.001
S5 > S2	<0.001
S5 > S3	0.01
S4 > S1	0.003
S4 > S2	<0.001
S3 > S1	0.050
S3 > S2	0.010

Table 3.3.2.10

Cardiac index did not change from when the patients were awake to the step after induction of anesthesia when two-lungs were being ventilated. However, cardiac index rose after initiation of OLA (S3) compared with both S1 and S2. Administration of all three dosages of dobutamine (S4,5 and 6) further increased cardiac output above values seen when the patients were awake (S1), above the cardiac index seen when two-lungs were being ventilated (S2), and above those levels seen during OLA when dobutamine was not being administered (S3).

Stroke index decreased during the step following initiation of anesthesia relative to steps 4. After initiation of OLA, this decrease in stroke index was restored to baseline awake state. No further changes in stroke index were seen while any of the dosages of dobutamine was being administered. However, heart rate increased on initiation of OLA and increased progressively as the dose of dobutamine was increased.

Dobutamine group												
	CVP (mmHg)			RVEDP (mmHg)			RVEDVI ($ml.m^{-2}$)			PAWP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	25	5.1	4.4	11	5.1	3.6	11	110	27	25	9.1	4.5
S2: Two-lung Anesthesia	24	6.5	4.1	12	7.0	3.4	9	100	25	24	9.8	4.2
S3: One Lung Anesthesia	24	7.0	37	10	7.4	3.0	12	112	23	24	11.3	4.1
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	6.5	3.8	9	7.1	2.8	8	101	20	18	10.4	3.6
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	7.2	3.5	10	8.7	3.7	10	116	42	16	8.6	5.3
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	6.8	3.8	5	8.4	4.2	11	114	19	15	10.6	4.0

Table 3.3.2.11

No intragroup changes in the indices of right or left ventricular preload occurred.

Dobutamine group															
	Ea PA (mmHg.ml^{-1})			PVR (dynes.secs.cm^{-5})			Rc PA[7] (dynes.secs.cm^{-5})			Rc PA[8] (dynes.secs.cm^{-5})			R TOTAL (dynes.secs.cm^{-5})		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	0.27	0.1	25	134	73	7	119	141	7	167	152	7	185	56
S2: Two-lung Anesthesia	24	0.31	0.1	24	145	77	7	115	100	7	143	117	7	254	146
S3: One Lung Anesthesia	23	0.29	0.07	23	119	54	7	57	49	7	84	52	7	185	21
S4: OLA & Dobutamine 3 ug.kg^{-1}.min^{-1}	18	0.28	0.1	18	117	50	8	66	39	8	61	66	8	138	58
S5: OLA & Dobutamine 5 ug.kg^{-1}.min^{-1}	17	0.34	0.09	16	162	52	5	66	96	5	108	98	5	202	61
S6: OLA & Dobutamine 7 ug.kg^{-1}.min^{-1}	20	0.35	0.1	15	125	48	6	76	55	6	76	80	6	154	48

Ea PA	p
S6 > S1	0.022

PVR	p
S5 > S3	0.043
S5 > S4	0.042
S5 > S6	0.045

Table 3.3.2.12

During OLA while dobutamine 5 ug.kg^{-1}.min^{-1} was being administered, PVR exceeded that observed during all other OLA steps. During OLA while dobutamine 7 ug.kg^{-1}.min^{-1} was being administered, pulmonary elastance (PA Ea) exceeded that observed when the patients were awake. No further intragroup changes in any of the other indices of pulmonary vascular resistance or impedance were observed in the dobutamine group.

[7] Calculated using Ro as derived using the Windkessel equation

[8] Calculated using Ea = R_{TOTAL}/time of the beat

Dobutamine group									
	Compliance PA[9] (ml.mmHg^{-1})			Compliance PA [10] (ml.mmHg^{-1})			Tau PA (secs)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	6	2.8	2.3	6	2.2	1.6	7	0.52	0.36
S2: Two-lung Anesthesia	6	3.3	1.6	6	3.0	1.3	6	0.65	0.34
S3: One Lung Anesthesia	6	3.5	2.1	6	3.1	1.9	6	0.49	0.26
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	7	3.7	2.9	7	4.1	2.5	6	0.46	0.23
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	5	2.1	0.8	5	2.1	0.5	5	0.34	0.14
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	5	1.1	0.5	5	1.2	0.5	5	0.19	0.09

Compliance PA using Rt/time	p
S5<S3	0.027
S6<S3	0.050

Tau	p
S6<S2	0.036

Table 3.3.2.13

During administration of dobutamine 7μg.kg^{-1}.min^{-1}, both PA compliance and the time constant of the pulmonary vasculature decreased. During the administration of 5 and 7μg.kg^{-1}.min^{-1} of dobutamine, PA compliance decreased significantly from that calculated during OLA when no dobutamine was being administered (S3).

[9] Calculated using Ro as derived using the Windkessel equation

[10] Calculated using Ea = R_{TOTAL}/time of the beat

Dobutamine group						
	SVR (dynes.secs.cm^{-5})			Ea Aorta (mmHg.ml^{-1})		
	n	□	SD.	n	□	SD.
S1: Awake	24	1282	345	24	1.4	0.5
S2: Two-lung Anesthesia	24	986	319	24	1.1	0.4
S3: One Lung Anesthesia	23	912	239	23	1.1	0.3
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	761	279	18	1.0	0.4
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	842	241	16	1.2	0.4
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	787	318	15	1.2	0.5

SVR	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001

Table 3.3.2.14

Both after induction of anesthesia and throughout OLA, systemic vascular resistance was less than that during the awake step.

No intragroup differences in aortic elastance were noted in the dobutamine group.

Dobutamine group									
	RVSWI ($g.m.m^{-2}$)			LVSWI ($g.m.m^{-2}$)			RVEF (%)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	9.1	3.8	25	52.4	18.7	12	41.2	6.7
S2: Two-lung Anesthesia	24	8.4	4.7	24	35.2	15.2	10	39.5	6.7
S3: One Lung Anesthesia	25	9.1	3.7	25	48.8	14.5	9	47.1	6.8
S4: OLA & Dobutamine 3 $_{ug.kg^{-1}.min^{-1}}$	18	13.0	5.5	18	52.4	22	12	44.8	6.4
S5: OLA & Dobutamine 5 $_{ug.kg^{-1}.min^{-1}}$	16	11.4	6.3	16	50.1	22.0	11	45.7	5.8
S6: OLA & Dobutamine 7 $_{ug.kg^{-1}.min^{-1}}$	15	13.3	6.8	15	50.0	16.3	9	45.9	4.6

RVSWI	p
S4 > S1	0.039
S4 > S2	0.024
S6 > S1	0.013
S6 > S2	0.022

LVSWI	p
S2 < S1	<0.001
S2 < S3	0.002
S2 < S4	<0.001
S2 < S5	0.004
S2 < S6	0.001

RVEF	p
S3 > S2	0.014
S4 > S2	0.020
S5 > S2	0.009
S6 > S2	0.012

Table 3.3.2.15

When compared with the awake step, no change in right ventricular stroke work index was seen either during the two-lung anesthesia (S2) or after the initiation of OLA (S3) steps. Dobutamine, at infusion rates of both 3 and 7 $\mu g.kg^{-1}.min^{-1}$, increased right ventricular stroke work index relative to steps 1 and 2. On administration of dobutamine 5 $\mu g.kg^{-1}.min^{-1}$, RVSWI did not differ from that seen during steps 1,2 or 3.

Left ventricular stroke work index decreased during the two-lung anesthesia step (S2) compared with the awake values. However, on commencement of surgery during the OLA step without administration of dobutamine (S3) and on administration of all 3 dosages of dobutamine, left ventricular stroke work index was restored to baseline levels.

No difference in right ventricular ejection fraction was seen on induction of anesthesia compared with the pre-induction levels. During both the baseline OLA step (S3) and during administration of all 3 dosages of dobutamine (S4,5 and 6), right ventricular ejection fraction increased compared with that seen during two-lung anesthesia (S2).

Dobutamine group												
	VO_2 index ($ml.min^{-1}.m^{-2}$)			DO_2 index ($ml.min^{-1}.m^{-2}$)			HKT (%)			Temperature (^oC)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	24	147	49	24	660	127	24	40.7	4.9	23	36.9	0.5
S2: Two-lung Anesthesia	23	90	28	23	613	169	23	36.2	4.9	21	36.0	0.6
S3: One Lung Anesthesia	23	100	30	23	759	206	23	35.7	6.4	23	35.9	0.6
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	18	119	32	18	896	199	18	36.1	7.1	18	35.9	0.6
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	16	121	27	16	803	195	16	34.3	5.3	16	35.9	0.6
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	15	113	31	15	892	217	15	33.7	6.0	14	35.9	0.7

VO_2 index	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S5 > S2	<0.002

DO_2 index	p
S2 < S3	0.001
S4 > S1	<0.001
S4 > S2	<0.001
S4 > S3	0.023
S5 > S1	0.007
S5 > S2	<0.001
S6 > S1	<0.001
S6 > S2	<0.001
S6 > S3	0.012

HKT	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001

Temperature	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001

Table 3.3.2.16

Oxygen consumption decreased by 39% after induction of anesthesia compared with when the patients were awake. Compared with awake levels, smaller decreases (23 to 32%) in oxygen consumption occurred on initiation of OLA (S3) and while dobutamine 3, 5 and 7 $\mu g.kg^{-1}.min^{-1}$ were administered.

After induction of anesthesia (S2), oxygen delivery was less than that seen during steps 3, 4, 5 and 6. However, the commencement of surgery and the initiation of OLA (S3), restored oxygen delivery to levels seen when the patients were awake. During the administration of dobutamine 3 and 7 $\mu g.kg^{-1}.min^{-1}$, oxygen delivery exceeded that seen during steps 1, 2 and 3. Dobutamine 5 $\mu g.kg^{-1}.min^{-1}$ increased oxygen delivery to levels that exceeded those observed when the patients were awake.

Compared with when the patients were awake, both hematocrit and temperature decreased after induction of anesthesia. These changes in hematocrit and temperature were sustained at similar levels as OLA progressed.

Dobutamine group						
	$CaO_2 - C\square O_2$ (ml.100ml^{-1})			OER		
	n	□	SD.	n	□	SD.
S1: Awake	24	4.07	1.20	24	0.22	0.06
S2: Two-lung Anesthesia	23	2.70	0.74	23	0.15	0.04
S3: One Lung Anesthesia	23	2.33	0.49	23	0.13	0.03
S4: OLA & Dobutamine 3 ug.kg^{-1}.min^{-1}	18	2.23	0.55	18	0.13	0.04
S5: OLA & Dobutamine 5 ug.kg^{-1}.min^{-1}	16	2.79	1.30	16	0.17	0.08
S6: OLA & Dobutamine 7 ug.kg^{-1}.min^{-1}	15	2.06	0.41	14	0.13	0.04

$CaO_2 - C\square O_2$	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001
S2 > S6	0.033
S5 > S6	0.048

OER	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S1 > S6	<0.001

Table 3.3.2.17

The arterial-venous oxygen content difference was decreased during the two-lung anesthesia step (S2) compared with when the patient was awake. This decrease was sustained on initiation of OLA (S3) and during administration of dobutamine 3μg.kg^{-1}.min^{-1}. However, on administration of dobutamine 7 μg.kg^{-1}.min^{-1}, the arterial-venous oxygen content difference was less than that seen during the infusion of dobutamine 5μg.kg^{-1}.min^{-1}, during two-lung anesthesia and while the patients were awake. The oxygen extraction ratio decreased by 30% after induction of anesthesia while two-lungs were being ventilated (S2) compared with when the patients were awake. Similar decreases in extraction ratio were seen during OLA (S3) and during administration of all dosages of dobutamine (S4, 5 and 6).

3.3.3 PEEP group tables

PEEP group						
	Tidal volume expired (ml.kg^{-1})			Minute volume expired (litres)		
	n	□	SD.	n	□	SD.
S1: Awake	-	-	-	-	-	-
S2: Two Lung Anesthesia, LDP	11	7.3	1.3	11	5.7	0.9
S3: After 15 minutes of OLA	11	6.2	1.5	11	4.8	0.9
S4: OLA, DL PEEP$_5$	11	6.2	1.4	11	4.7	1.3
S5: OLA, DL PEEP$_{10}$	6	5.8	0.4	6	4.9	1.2

Minute volume	p
S2 > S3	0.014
S2 > S4	0.009
S2 > S5	0.060

Table 3.3.3.1

No changes in expired tidal volume were seen on institution of OLA. No changes in tidal volume were observed during OLA when either 5 or 10 cm H_2O PEEP was applied to the dependant lung.

However, expired minute volume decreased on institution of OLA compared with that measured during two-lung anesthesia. This decrease was sustained during administration of PEEP$_5$ to the dependant lung.

However, the expired minute volume during the PEEP$_{10}$ step did not differ statistically from that measured during S2, S3 or S5.

PEEP group									
	Peak airway pressure ($cm\ H_20$)			Dynamic compliance ($ml.cm\ H_20^{-1}$)			Intrinsic PEEP ($cm\ H_20$)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	-	-	-	-	-	-	-	-	-
S2: Two Lung Anesthesia, LDP	11	21	6.4	11	25	9.0	2	1	1
S3: After 15 minutes of OLA	11	31	8.3	11	15	6.5	2	2.5	2.5
S4: OLA, DL $PEEP_5$	11	34	8.1	11	14	4.7	1	11	0
S5: OLA, DL $PEEP_{10}$	6	40	7.2	6	12	3.4	1	10	0

Peak airway pressure	p
S3 > S2	<0.001
S4 > S2	<0.001
S5 > S2	<0.001
S5 < S3	0.062

Dynamic compliance	p
S3 < S2	<0.001
S4 < S2	<0.001
S5 < S2	<0.001

Table 3.3.3.2

Peak airway pressure increased by 48% and dynamic compliance decreased by 40% on initiation of OLA compared with when two lungs were being ventilated. Administration of both $PEEP_5$ (S4) and $PEEP_{10}$ (S5) also resulted in an increased peak airway pressure and decreased dynamic compliance compared with that seen during two-lung anesthesia (S2).

No intragroup differences in PEEPi were observed.

PEEP group			
	End tidal isoflurane (kPa)		
	n	□	SD.
S1: Awake	-	-	-
S2: Two Lung Anesthesia, LDP	4	0.4	0.1
S3: After 15 minutes of OLA	4	0.5	0.1
S4: OLA, DL $PEEP_5$	3	0.6	0.2
S5: OLA, DL $PEEP_{10}$	4	0.5	0.1

Table 3.3.3.3

No differences in the end tidal partial pressure of isoflurane occurred between the various steps of the PEEP group.

PEEP group	$PaCO_2$ (kPa)			$PeCO_2$ (kPa)			pH arterial			HCO_{37} (mmol.litre^{-1})			B.E. (mmol.litre^{-1})		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	4.9	0.3	-	-	-	10	7.43	0.02	10	25.8	2.4	10	1.2	2.4
S2: Two Lung Anesthesia, LDP	11	5.2	0.5	11	4.2	0.9	11	7.41	0.05	11	26.1	2.4	11	0.9	2.7
S3: After 15 minutes of OLA	11	5.5	0.7	11	4.7	1.0	11	7.39	0.06	11	25.9	1.9	11	0.2	2.6
S4: OLA, DL $PEEP_5$	11	5.7	0.8	11	4.9	1.2	11	7.35	0.06	11	24.9	2.2	11	-1.4	2.5
S5: OLA, DL $PEEP_{10}$	6	6.0	0.8	6	5.0	0.8	6	7.35	0.06	6	26.2	1.6	6	-0.5	1.8

$PaCO_2$	p
S1 < S3	0.024
S1 < S4	0.003
S1 < S5	0.009
S2 < S4	0.050

$PeCO_2$	p
S2 < S4	0.016

pH arterial	p
S1 > S3	0.006
S1 > S4	<0.001
S1 > S5	<0.001
S2 > S4	<0.001
S2 > S5	0.002
S3 > S4	0.011
S3 > S5	0.054

B.E.	p
S1 > S4	<0.001
S1 > S5	0.003
S2 > S4	0.001
S2 > S5	0.006
S3 > S5	0.034
S3 > S4	0.034

Table 3.3.3.4

Arterial carbon dioxide tension did not differ between when the patients were awake (S1) and two-lung anesthesia (S2). However, arterial carbon dioxide tension increased on initiation of OLA (S3) compared with when the patients were awake (S1). This increase was sustained during application of both $PEEP_5$ and $PEEP_{10}$ to the dependant lung. During the $PEEP_5$ (S4) step, $PeCO_2$ was also greater than during the two-lung anesthesia step (S2).

Arterial pH decreased on institution of OLA (S3) compared to the awake state (S1). Progressive decreases in arterial pH occurred during steps 3,4 and 5 of the PEEP group. No differences between bicarbonate concentrations occurred between any steps in the PEEP group. Base excess decreased on administration of both levels of PEEP compared to all of the first 3 steps of the PEEP group.

PEEP group												
	PaO_2 (kPa)			SaO_2 (%)			$P□O_2$ (kPa)			$S□O_2$ (%)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	11.6	2.2	10	97.0	2.1	10	5.4	0.4	10	74.6	4.5
S2: Two Lung Anesthesia, LDP	11	54.4	13.5	11	99.9	0.04	11	8.3	1.3	11	89.9	4.0
S3: After 15 minutes of OLA	11	43.2	21.8	11	97.9	4.0	11	8.4	1.7	11	88.9	7.1
S4: OLA, DL $PEEP_5$	11	39.5	21.9	11	97.8	4.0	11	8.3	2.2	11	86.8	7.9
S5: OLA, DL $PEEP_{10}$	6	25.3	16.1	6	95.7	7.7	6	6.6	1.3	6	79.0	9.4

PaO_2	p
S2> S1	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	0.004
S2 > S3	0.024
S2 > S4	0.009
S2 > S5	0.005

$P□O_2$	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	0.001

$S□O_2$	p
S1 < S2	<0.001
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	0.005
S2 > S5	0.010
S3 > S5	0.017

Table 3.3.3.5

Arterial oxygen tension was less when the patients were awake than in all other steps. During two-lung anesthesia, arterial oxygen tension exceeded that in all other steps. However, no intragroup differences in arterial oxygen saturation were observed.

Both mixed venous oxygen tension and saturation increased after induction of anesthesia (S2). This increase was sustained on initiation of OLA (S3) and when $PEEP_5$ (S4) was administered. However, mixed venous oxygen saturation decreased to levels not different from baseline when $PEEP_{10}$ (S5) was administered compared with both OLA without PEEP (S3) and two-lung anesthesia (S2).

PEEP group						
	CaO_2 ($ml.100ml^{-1}$)			$C\square O_2$ ($ml.100ml^{-1}$)		
	n	□	SD.	n	□	SD.
S1: Awake	10	17.7	2.0	10	13.5	1.9
S2: Two Lung Anesthesia, LDP	11	17.0	1.6	11	14.3	1.3
S3: After 15 minutes of OLA	11	16.8	1.6	11	14.5	1.4
S4: OLA, DL $PEEP_5$	11	15.5	2.1	11	13.0	1.7
S5: OLA, DL $PEEP_{10}$	6	16.4	1.8	6	13.1	1.4

CaO_2	p
S1 > S4	0.014
S2 > S4	0.061
S3 > S4	0.061

Table 3.3.3.6

No intragroup difference in mixed venous oxygen content occurred. However, arterial oxygen content was decreased compared to the awake baseline state while $PEEP_5$ (S4) was being administered.

PEEP group									
	Shunt Qs/Qt %			$D(A\text{-}a)O_2$			PaO_2/FiO_2		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	14.2	8.1	10	7.4	2.2	10	55.0	10.6
S2: Two Lung Anesthesia, LDP	11	26.2	8.5	11	40.7	13.5	11	54.4	13.5
S3: After 15 minutes of OLA	11	36.1	14.8	11	51.8	21.8	11	43.2	21.8
S4: OLA, DL $PEEP_5$	11	36.4	12.6	11	55.5	21.9	11	39.5	21.9
S5: OLA, DL $PEEP_{10}$	6	39.0	12.7	6	69.7	16.1	6	25.3	16.1

Shunt	p
S1 < S2	0.002
S1 < S3	<0.001
S1 < S4	<0.001
S1 < S5	<0.001
S3 > S2	0.032
S4 > S2	0.047
S5 vs. S2	0.059

PaO_2/FiO_2	p
S1 > S2	<0.001
S1 > S3	0.001
S1 > S4	0.012
S1 > S5	0.003
S2 > S3	0.003
S2 > S4	0.009
S2 > S5	0.008

$D(A\text{-}a)O_2$	p
S2 > S1	<0.001
S3 > S1	<0.001
S4 > S1	<0.001
S5 > S1	<0.001
S3 > S2	0.024
S4 > S2	0.009
S5 > S2	0.005

Table 3.3.3.7

The shunt fraction increased after induction of anesthesia while 2 lungs were being ventilated (S2) compared with the awake state (S1). Shunt fraction further increased on initiation of OLA (S3) compared with the preceding two steps (S1 and S2). A similar increase in shunt fraction was also apparent while $PEEP_5$ was applied to the dependent lung (S4) compared with both the awake and two lung anesthesia steps (S1 and S2). Shunt during $PEEP_{10}$ (S5) was also greater than when the patients were awake (S1), but did not differ from that measured during the two lung anesthesia step (S2).

The $D(A\text{-}a)O_2$ increased while the PaO_2/FiO_2 ratio decreased after induction of anesthesia. The cost of oxygenation increased even further as indicated by further increases in the $D(A\text{-}a)O_2$ and decreases in the PaO_2/FiO_2 ratio during OLA (S3), or when $PEEP_5$ (S4) or $PEEP_{10}$ (S5) were applied to the dependant lung, compared with both the awake (S1) and two lung anesthesia steps (S2).

PEEP group												
	MAP (mmHg)			Systemic Pes (mmHg)			SAP (mmHg)			DAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	98.5	7.8	9	98.4	9.1	10	144.4	13.7	10	75.6	6.6
S2: Two Lung Anesthesia, LDP	11	80.5	19.5	10	80.6	14.9	11	111.3	26.4	11	65.1	16.3
S3: After 15 minutes of OLA	11	86.9	17.7	10	87.8	17.3	11	122.5	26.9	11	69.2	13.4
S4: OLA, DL $PEEP_5$	10	70.9	15.1	10	69.3	16.6	10	100.7	24.2	10	56.1	10.9
S5: OLA, DL $PEEP_{10}$	5	74.3	12.9	5	72.8	14.4	5	104.6	19.7	5	59.2	9.7

MAP	p
S1 > S5	0.016
S1 > S4	0.002

Systemic Pes	p
S1 > S4	<0.001
S1 > S5	0.004
S1 > S2	0.022
S3 > S4	0.013
S3 > S5	0.044

SAP	p
S1 > S5	0.003
S1 > S4	<0.001
S1 > S2	0.008

DAP	p
S1 > S4	0.005

Table 3.3.3.8

During both steps during which PEEP was administered, MAP, Pes and SAP decreased compared to when the patients were awake. Both SAP and Pes were less during the two-lung anesthesia step than during the awake step. DAP was less during the $PEEP_5$ step than when the patients were awake.

PEEP group									
	PAP (mean) (mmHg)			SPAP (mmHg)			DPAP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	20.2	4.3	10	34.8	6.9	10	12.9	3.6
S2: Two Lung Anesthesia, LDP	11	18.6	4.4	11	28.4	6.7	11	13.7	3.9
S3: After 15 minutes of OLA	11	20.3	10.1	11	35.3	12.6	11	15.9	5.9
S4: OLA, DL $PEEP_5$	10	22.0	4.0	10	35.5	6.8	10	15.3	3.2
S5: OLA, DL $PEEP_{10}$	5	24.9	2.4	5	40.6	6.1	5	17.0	2.3

Table 3.3.3.9

No intragroup changes in mean, systolic or diastolic pulmonary arterial pressures were noted in the PEEP group.

PEEP group									
	Cardiac index (litres.min^{-1}.m^{-2})			Stroke index (ml.min^{-1}.m^{-2})			Heart rate (beats.min^{-1})		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	3.7	0.7	10	48	14	10	80	23.4
S2: Two Lung Anesthesia, LDP	11	3.1	0.9	11	38	7	11	81	18.8
S3: After 15 minutes of OLA	11	4.1	1.2	11	47	13	11	89	17.8
S4: OLA, DL $PEEP_5$	11	4.0	1.2	11	42	9	10	95	14.0
S5: OLA, DL $PEEP_{10}$	6	3.0	0.9	5	34	8	5	90	9.7

Cardiac index	p
S2 < S3	0.020
S2 < S4	0.031
S5 vs. S4	0.089

Stroke index	p
S5 < S1	0.018
S5 < S3	0.031
S2 < S1	0.029

Table 3.3.3.10

Cardiac index did not differ during two-lung anesthesia compared with when the patients were awake. Cardiac index increased on initiation of OLA (S3) compared with when two lungs were being ventilated

(S2). This rise was sustained while $PEEP_5$ (S4) was being administered. Cardiac index did not differ statistically from step one while $PEEP_{10}$ (S5) was being administered. On administration of $PEEP_{10}$, (S5) cardiac index did not differ from that measured during steps 1 or 2.

Stroke index decreased during two-lung anesthesia (S2) compared with when the patients were awake (S1). On initiation of OLA (S3), and while $PEEP_5$ (S4) was being administered, stroke index did not differ from when the patients were awake. However, the administration of DL $PEEP_{10}$ (S5) decreased stroke index compared with both when the patients were awake (S1) and that calculated for the OLA (S3) step. During administration of $PEEP_{10}$ (S5), stroke index did not differ from that seen during S2, S3 or S4.

No intragroup changes in heart rate were observed.

PEEP group												
	CVP (mmHg)			RVEDP (mmHg)			RVEDVI ($ml.m^{-2}$)			PAWP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	5.3	2.3	6	6.7	3.2	10	112	26.0	10	10.2	4.3
S2: Two Lung Anesthesia, LDP	11	5.0	2.6	7	9.3	2.7	11	107	18.6	9	9.2	4.3
S3: After 15 minutes of OLA	11	6.3	3.0	7	11.3	4.2	11	109	28.0	10	10.3	3.6
S4: OLA, DL $PEEP_5$	10	6.4	3.7	8	8.1	2.2	10	97	21.5	10	11.4	2.7
S5: OLA, DL $PEEP_{10}$	5	5.4	2.6	4	10.3	3.6	6	83	22.6	5	9.4	2.2

RVEDVI	p
S5 < S1	0.008
S5 < S2	0.024
S5 < S3	0.014

Table 3.3.3.11

No intragroup changes in filling pressures of either the right or left ventricle occurred in the PEEP group. However, compared to steps 1, 2 and 3, a significant decrease in right ventricular end-diastolic volume index occurred when $PEEP_{10}$ was administered to the dependant lung.

PEEP group															
	Ea PA (mmHg.ml^{-1})			PVR (dynes.secs.cm^{-5})			Rc PA[11] (dynes.secs.cm^{-5})			Rc PA[12] (dynes.secs.cm^{-5})			R TOTAL (dynes.secs.cm^{-5})		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	0.27	0.1	10	133	63	10	167	52	10	151	128	10	244	178
S2: Two Lung Anesthesia, LDP	11	0.30	0.1	9	147	70	9	143	77	9	130	112	9	250	129
S3: After 15 minutes of OLA	11	0.29	0.08	9	124	52	9	104	49	9	74	50	9	176	52
S4: OLA, DL $PEEP_5$	10	0.34	0.10	10	155	60	10	104	57	10	65	41	10	200	66
S5: OLA, DL $PEEP_{10}$	7	0.36	0.08	7	177	57	7	135	69	7	80	45	7	206	60

Ea PA	p
S4 > S1	0.03
S5 > S1	0.002
S5 > S2	0.047
S5 > S3	0.030

PVR	p
S5 > S1	0.018
S5 > S3	0.030

Rc PA = Rt/time	p
S1 > S4	0.048

Table 3.3.3.12

During steps 2 and 3, PA elastance did not differ from the awake step. However, administration of $PEEP_5$ to the dependant lung (S4) increased PA elastance, but at the same time decreased characteristic impedance compared to baseline awake levels (S1). The administration of 10 cm of water of PEEP to the dependant lung (S5) also increased PA elastance compared to the awake (S1), two lung anesthesia (S2) and OLA steps when PEEP was not applied (S3). $PEEP_{10}$ (S5) also increased pulmonary vascular resistance during OLA compared to both the awake (S1) and OLA step when PEEP was not applied (S3).

[11] Calculated using Ro as derived using the Windkessel equation

[12]. Calculated using Ea = R_{TOTAL}/time of the beat

PEEP group									
	Compliance PA[13] (ml.mmHg^{-1})			Compliance PA [14](ml.mmHg^{-1})			Tau PA (secs)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	9	2.8	1.9	9	2.2	1.4	13	0.46	0.3
S2: Two Lung Anesthesia, LDP	8	2.7	1.3	8	2.4	1.1	10	0.52	0.29
S3: After 15 minutes of OLA	8	3.4	2.4	8	2.9	2.2	11	0.43	0.24
S4: OLA, DL $PEEP_5$	9	2.5	1.0	9	2.5	0.6	9	0.35	0.12
S5: OLA, DL $PEEP_{10}$	7	2.1	1.1	7	1.9	1.0	7	0.36	0.16

Table 3.3.3.13

No intragroup changes in PA compliance or the time constant of the pulmonary circulation were observed in the PEEP group.

[13] Calculated using Ro as derived using the Windkessel equation

[14] Calculated using Ea = R_{TOTAL}/time of the beat

PEEP group						
	SVR (dynes.secs.cm^{-5})			Ea Aorta (mmHg.ml^{-1})		
	n	□	SD.	n	□	SD.
S1: Awake	10	1251	414	10	1.4	0.5
S2: Two Lung Anesthesia, LDP	11	1221	271	11	1.1	0.3
S3: After 15 minutes of OLA	11	1047	478	11	1.1	0.3
S4: OLA, DL PEEP$_5$	11	693	322	11	1.1	0.5
S5: OLA, DL PEEP$_{10}$	5	960	124	5	1.1	0.3

SVR	p
S4 < S1	0.003
S4 < S2	0.003
S5 < S1	0.004
S5 < S2	0.036

Table 3.3.3.14

Systemic vascular resistance showed no decrease after induction of anesthesia or initiation of OLA compared to the awake state. However, administration of both DL PEEP$_5$ (S4) and DL PEEP$_{10}$ (S5) decreased systemic vascular resistance compared to values calculated for the baseline awake (S1) and two lung anesthesia steps (S2).

No intragroup changes in aortic elastance were observed in the PEEP group.

PEEP group									
	RVSWI ($g.m.m^{-2}$)			LVSWI ($g.m.m^{-2}$)			RVEF (%)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	10.5	.2	10	47	12	4	41.7	8.1
S2: Two Lung Anesthesia, LDP	11	7.7	2.6	11	45	12	4	43.5	7.7
S3: After 15 minutes of OLA	11	10.8	4.7	11	43	12	4	36.0	7.0
S4: OLA, DL $PEEP_5$	11	9.8	4.4	11	45	19	4	41.0	4.2
S5: OLA, DL $PEEP_{10}$	5	9.5	2.7	5	31	17	3	35.9	8.7

LVSWI	p
S5 < S1	0.010
S5 < S2	0.034
S5 < S4	0.020
S5 < S2	0.031

Table 3.3.3.15

No intragroup changes in either right ventricular stroke work index or right ventricular ejection fraction were observed.

Left ventricular stroke work index did not change either during two-lung ventilation or after initiation of OLA or on application of DL $PEEP_5$. However, administration of DL $PEEP_{10}$ decreased left ventricular stroke work index compared with that calculated for the step when two lungs were being ventilated (S2).

PEEP group												
	VO_2 index ($ml.min^{-1}.m^{-2}$)			DO_2 index ($ml.min^{-1}.m^{-2}$)			HKT (%)			Temperature (^oC)		
	n	□	SD.	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	151	34.4	10	645	126	10	38.7	4.4	9	36.7	0.8
S2: Two Lung Anesthesia, LDP	11	78	19.4	11	526	201	11	34.0	3.9	10	36.1	0.8
S3: After 15 minutes of OLA	11	94	31.6	11	690	201	11	35.1	5.2	11	35.8	0.7
S4: OLA, DL $PEEP_5$	11	97	28.9	11	621	177	11	32.4	6.7	11	35.8	1.2
S5: OLA, DL $PEEP_{10}$	6	102	39.3	6	511	183	6	36.0	6.4	6	36.0	1.0

VO_2 index	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001

DO_2 index	p
S5 < S3	0.049
S2 < S3	0.008

HKT	p
S1 > S2	0.021
S1 > S3	0.031
S1 > S4	0.002

Temperature	p
S1 > S2	0.025
S1 > S3	0.007
S1 > S4	0.021

Table 3.3.3.16

Compared with the awake state (S1), oxygen consumption was decreased after induction of anesthesia (S2). After initiation of OLA (S3) and during application of both levels of PEEP to the DL (S4 and S5), oxygen consumption was less than when the patients were awake (S1).

Delivery of oxygen was less while two lungs were being ventilated (S2) than after initiation of OLA (S3). On administration of DL $PEEP_{10}$, oxygen delivery also decreased to values less than those observed during OLA when PEEP was not being applied (S3).

Hematocrit and temperature was greater when the patients were awake than in all but the last step (S5) of the PEEP group.

PEEP group									
	$CaO_2 - C\square O_2$ (ml.100ml^{-1})			OER			RV CPP (mmHg)		
	n	□	SD.	n	□	SD.	n	□	SD.
S1: Awake	10	4.1	0.7	10	0.24	0.04	10	76	13
S2: Two Lung Anesthesia, LDP	11	2.7	0.8	11	0.16	0.04	11	53	15
S3: After 15 minutes of OLA	11	2.3	0.5	11	0.14	0.03	11	62	17
S4: OLA, DL $PEEP_5$	11	2.5	0.5	11	0.16	0.02	11	46	16
S5: OLA, DL $PEEP_{10}$	6	3.3	0.8	6	0.20	0.03	6	43	15

$CaO_2 - C\square O_2$	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	<0.001
S5 vs. S3	0.085

OER	p
S1 > S2	<0.001
S1 > S3	<0.001
S1 > S4	<0.001
S1 > S5	0.004
S5 > S3	0.013
S5 vs. S3	0.066

RV CPP during OLA	p
S5 < S1	<0.001
S5 < S3	<0.001
S5 < S4	<0.001
S4 < S1	<0.001

Table 3.3.3.17

The arterial-venous oxygen content difference decreased after induction of anesthesia (S2) and during both OLA (S3) and administration of DL $PEEP_5$ (S4) compared to when the patients were awake (S1). Administration of $PEEP_{10}$ increased the numerical value of the arterial-venous oxygen content difference to its highest level observed during anesthesia in any of the groups. This increase however was not statistically significant.

The oxygen extraction ratio was decreased after induction of anesthesia (S2) compared with when the patients were awake. This decrease was sustained during both OLA (S3), and during the OLA DL $PEEP_5$ step (S4). However on application of $PEEP_{10}$ to the dependant lung (S5), the oxygen extraction ratio did not differ from the awake state.

On application of DL $PEEP_{10}$, RV coronary perfusion pressure decreased when compared to the awake, OLA and DL $PEEP_5$ steps. $PEEP_5$ decreased RV coronary perfusion pressure compared to when the patients were awake.

3.4 Within group comparisons (graphically represented)

Data is presented as the mean value for that step. The error bars represent the 95% confidence intervals. Any differences between the steps determined by RM ANOVA and utilizing Student-Neuman-Keuls' test for post hoc analysis are annotated in the caption of the figure.

3.4.1 Control group

Steps in control group patients	Label
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA
15 minutes after commencing one lung ventilation	S3: OLA 15 mins
5 minutes after step 3 data had been recorded	S4: OLA Control 1
5 minutes after step 4 data had been recorded	S5: OLA Control 2
5 minutes after step 5 data had been recorded	S6: OLA Control 3
5 minutes after step 6 data had been recorded	S7: OLA Control 4

Table 3.4.1.1 The sequence of the steps and abbreviations used in the control group graphs.

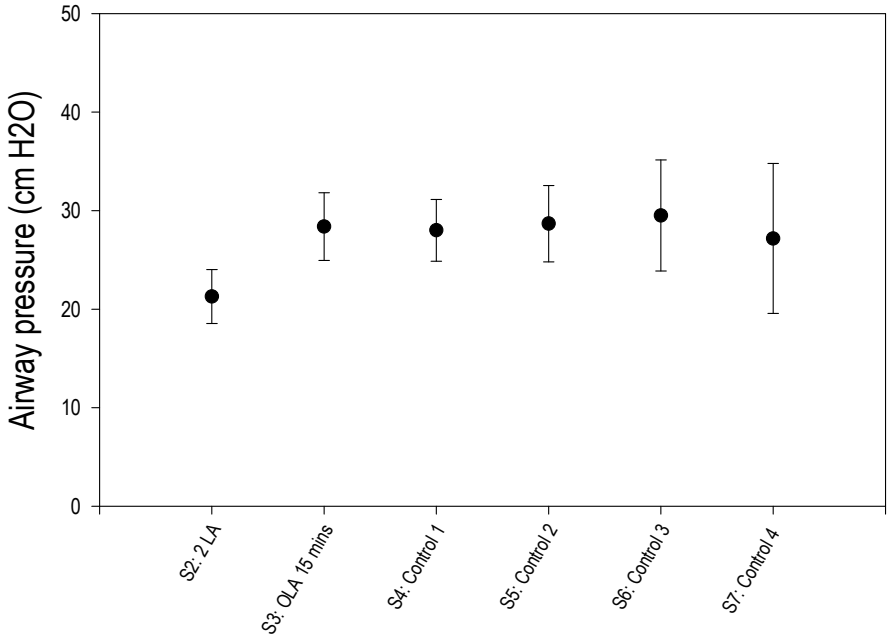


Figure 3.4.1.1 Airway pressure, Control group
S2 < S3,4,5,6

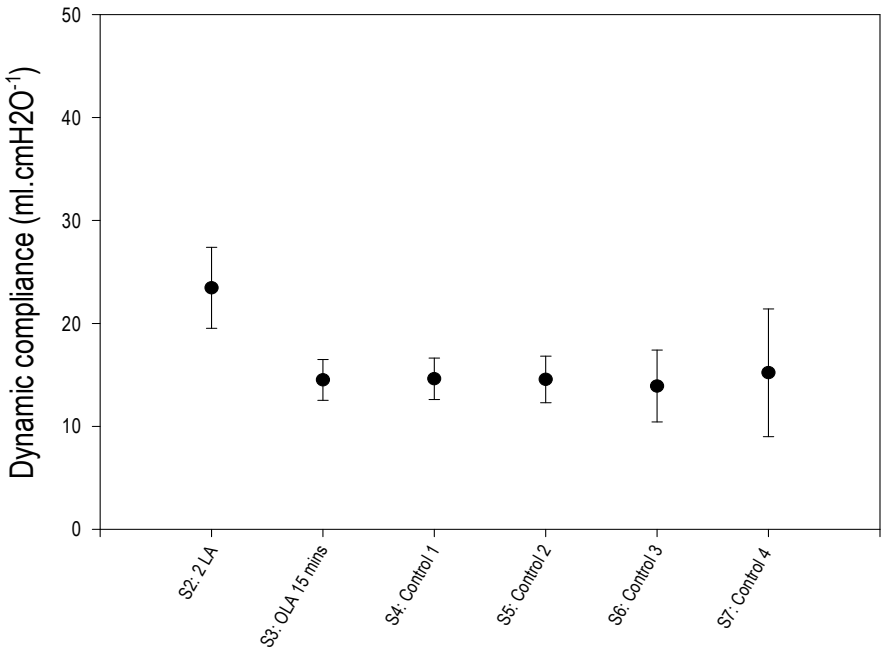


Figure 3.4.1.2 Dynamic compliance, Control group
S2 > S3,4,5,6,7

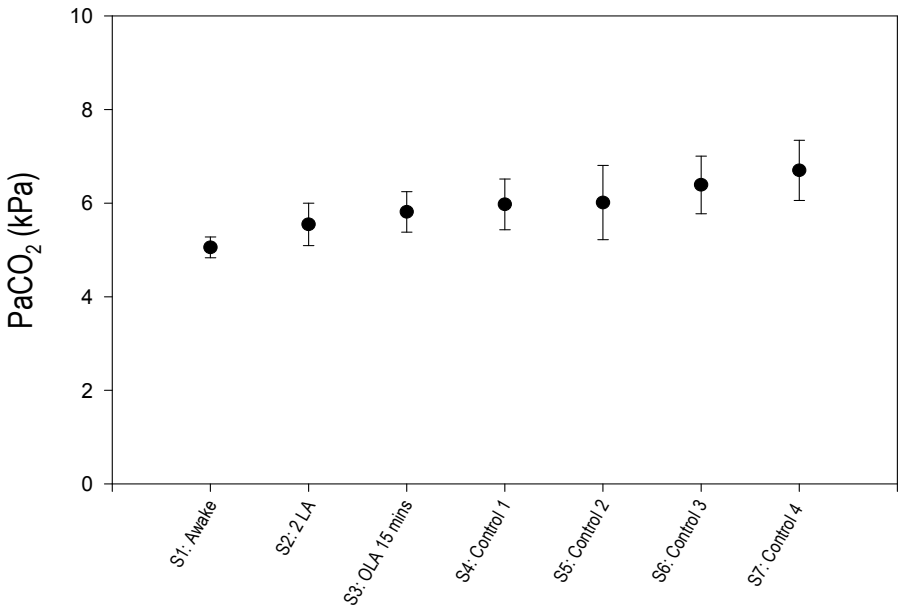


Figure 3.4.1.3 $PaCO_2$, Control group
S1 < S4, 5, 6, 7 S2 < S5, 7

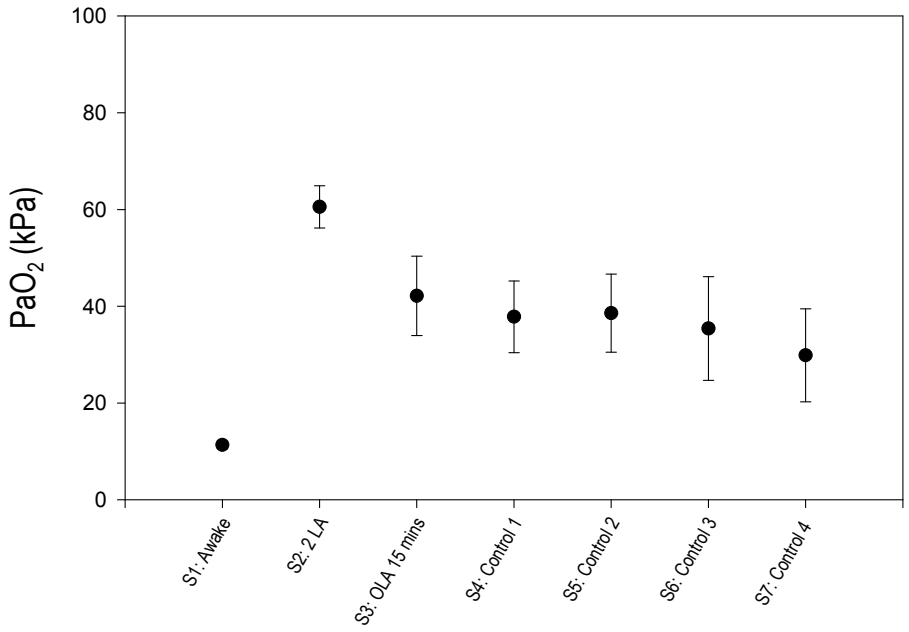


Figure 3.4.1.4 PaO_2, Control group
S1 < S2,3,4,5 S2 > S1,3,4,5,6,7

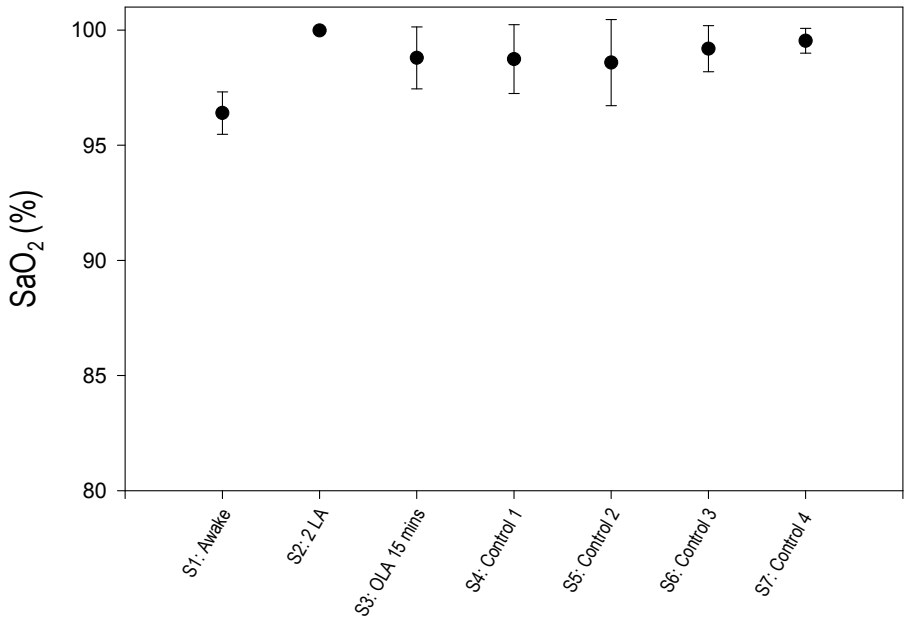


Figure 3.4.1.5 Arterial oxygen saturation, Control group
S1 < S2,4,5,7

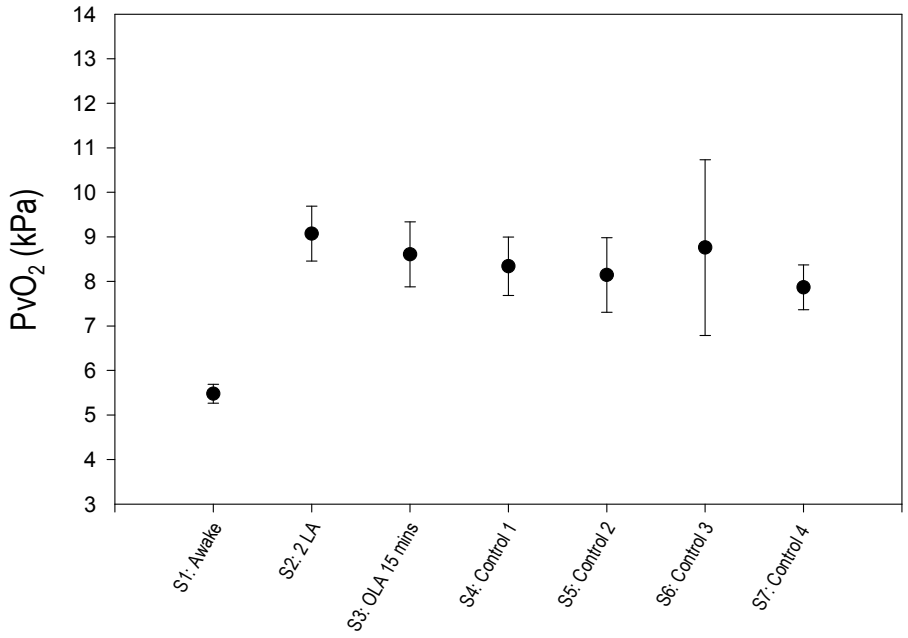


Figure 3.4.1.6 PvO_2, Control group
S1 < S2,3,6,7

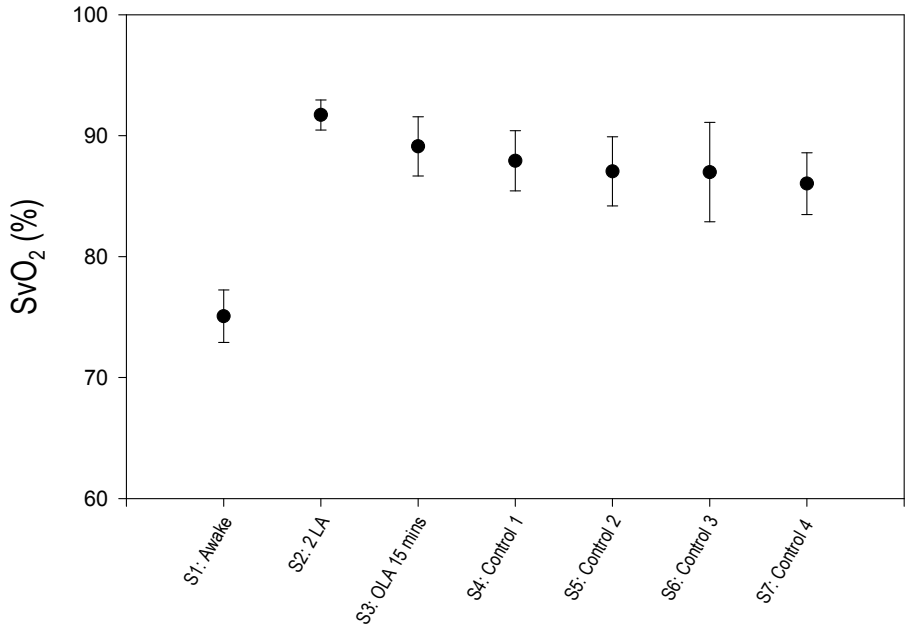


Figure 3.4.1.7 SvO_2, Control group
S1 < S2,3,4,5 S2 < S6

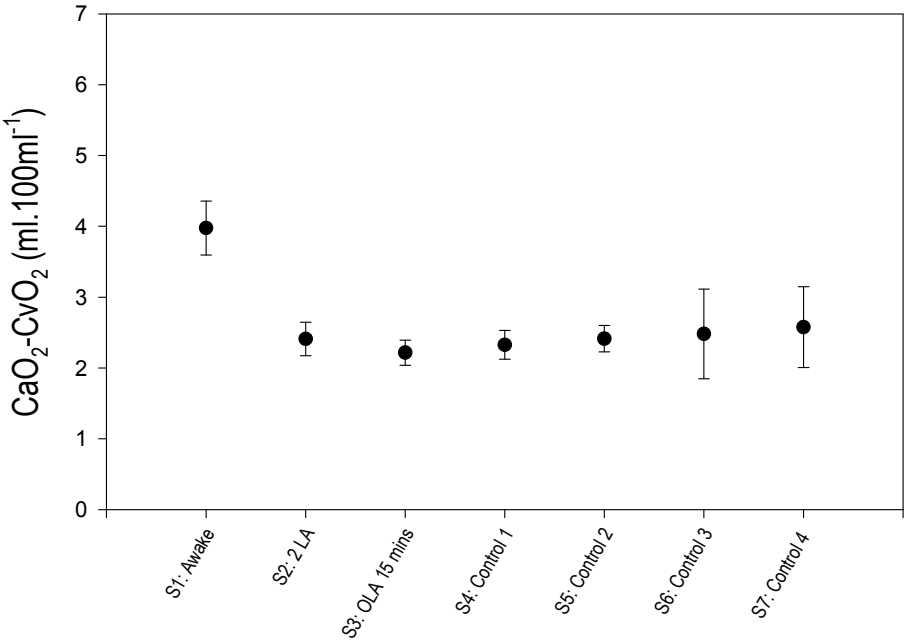


Figure 3.4.1.8 CaO_2-CvO_2, Control group
S1 > S2,3,4,5,6,7

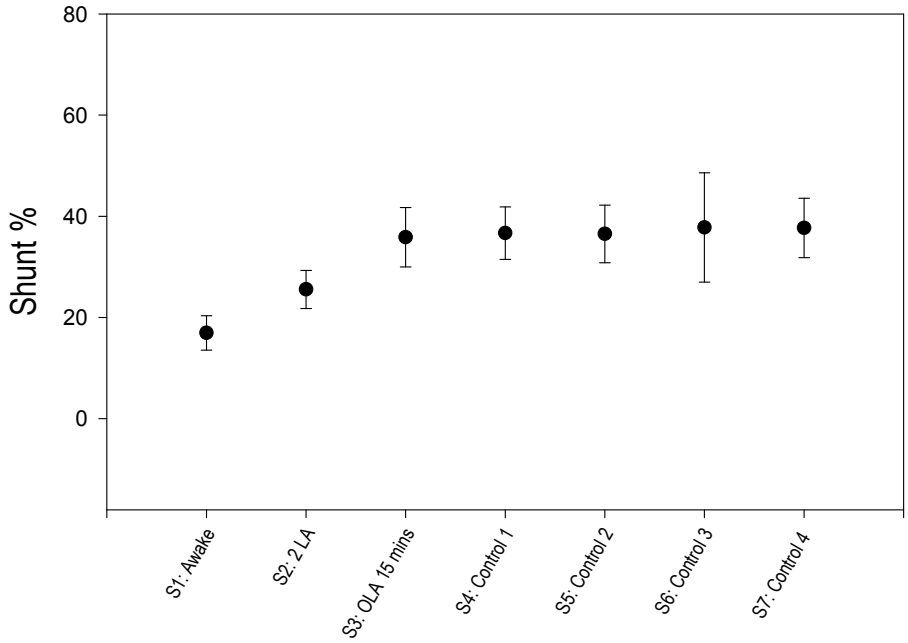


Figure 3.4.1.9 Shunt, Control group
S1 < S4,5,6,7 S2 < S4,5,6

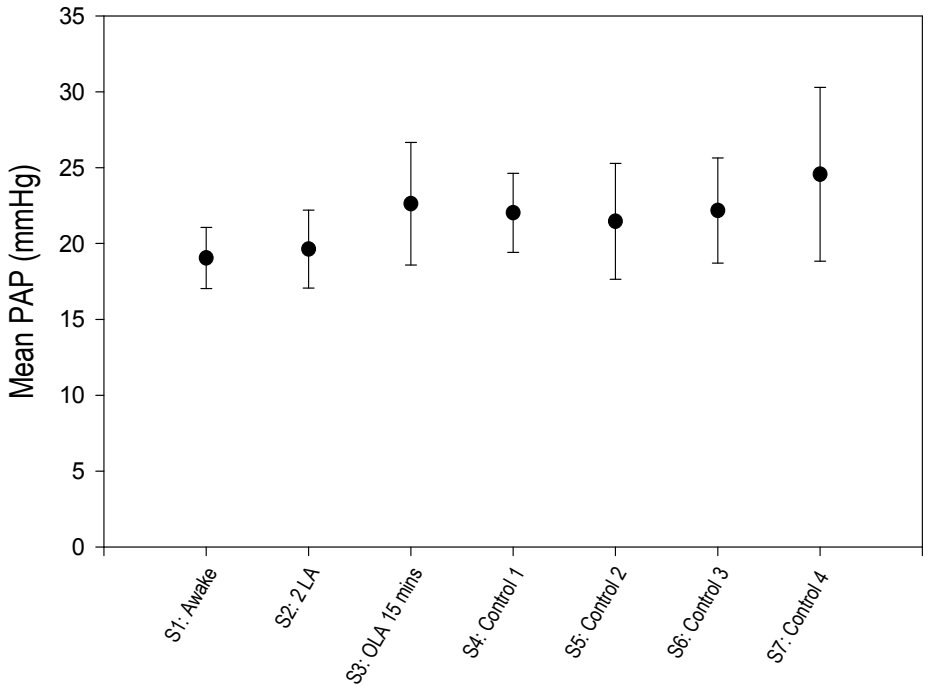


Figure 3.4.1.10 Mean PAP, Control group
S1 <S3,5,6,7 S2 < S3,5,7

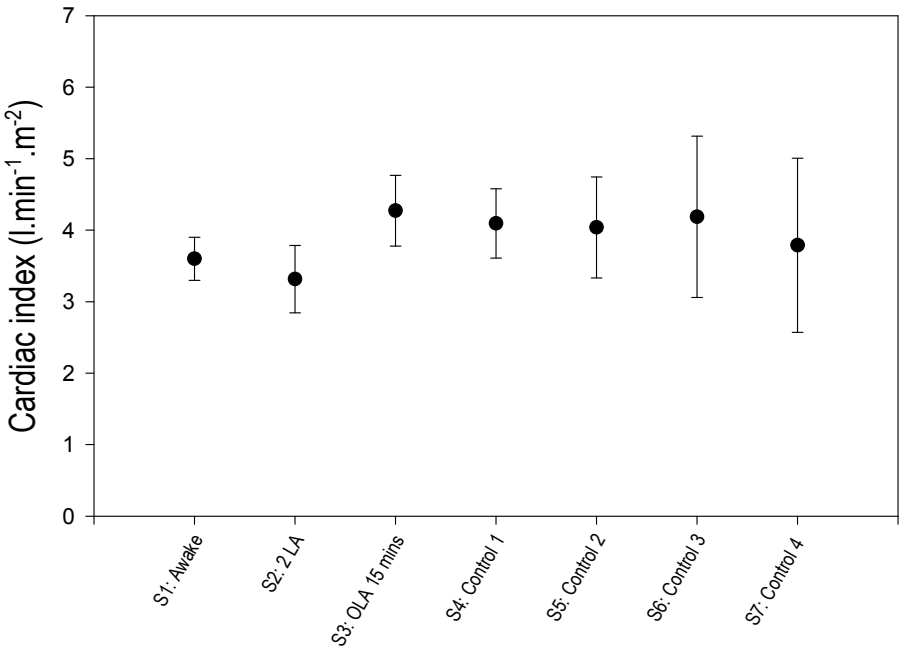


Figure 3.4.1.11 Cardiac index, Control group
S1 < S3 S2 < S3,4,5,6

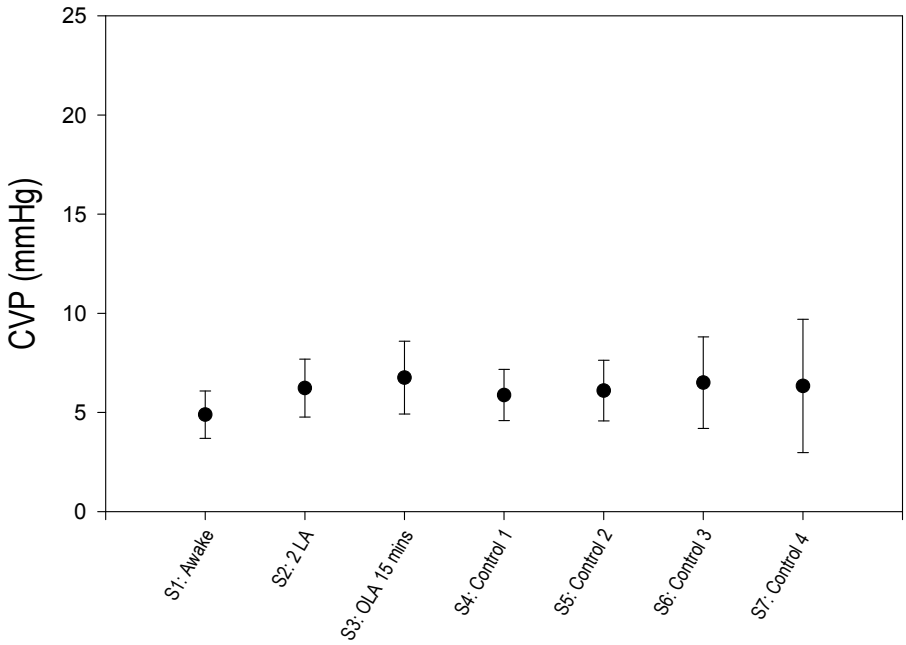


Figure 3.4.1.12 CVP, Control group

Note that the "y" axis ranges from 0 to 25 mm Hg to allow both left and right-sided filling pressures (i.e. PAWP and CVP) to be illustrated on the same scale.

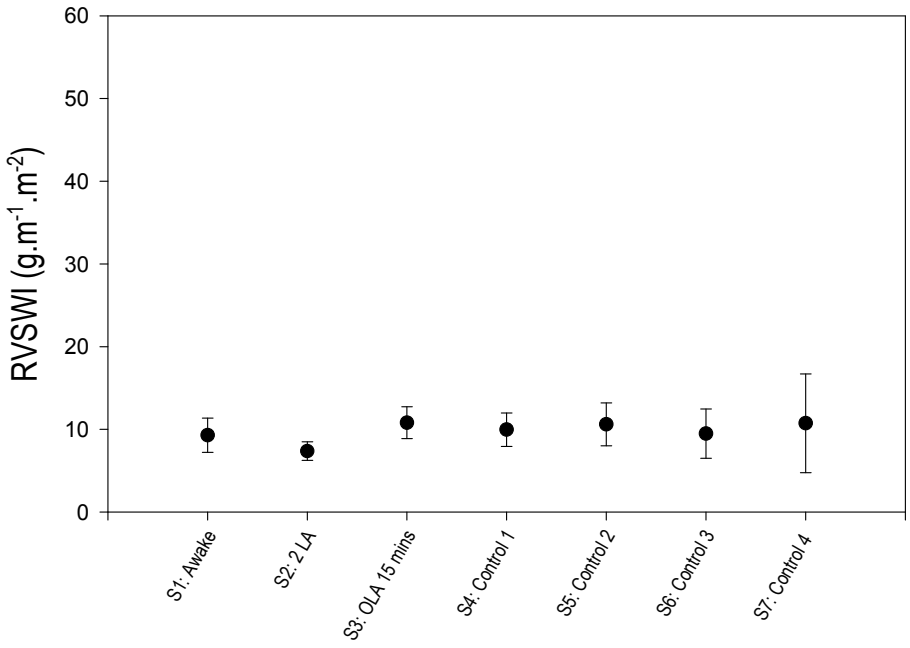


Figure 3.4.1.13 RVSWI, Control group

Note that the "y" axis ranges from 0 to 60 g.m.m^{-2} to give the perspective of how much less stroke work the RV generates compared with its counterpart, the LV. LVSWI ranges from 45 to 60 g.m.m^{-2} whereas RVSWI is approximately 8 to 10 g.m.m^{-2}.

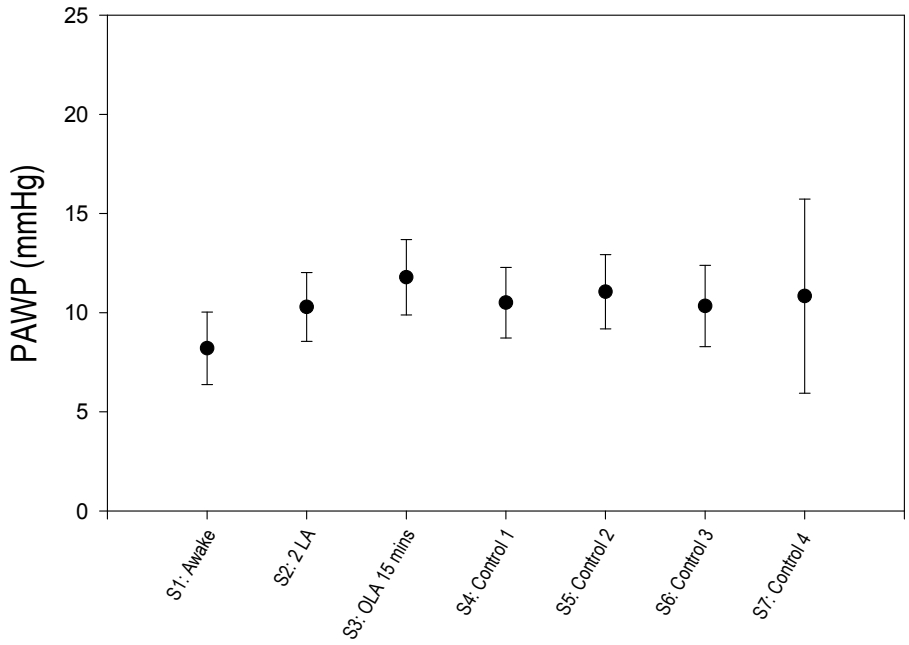


Figure 3.4.1.14 PAWP, Control group

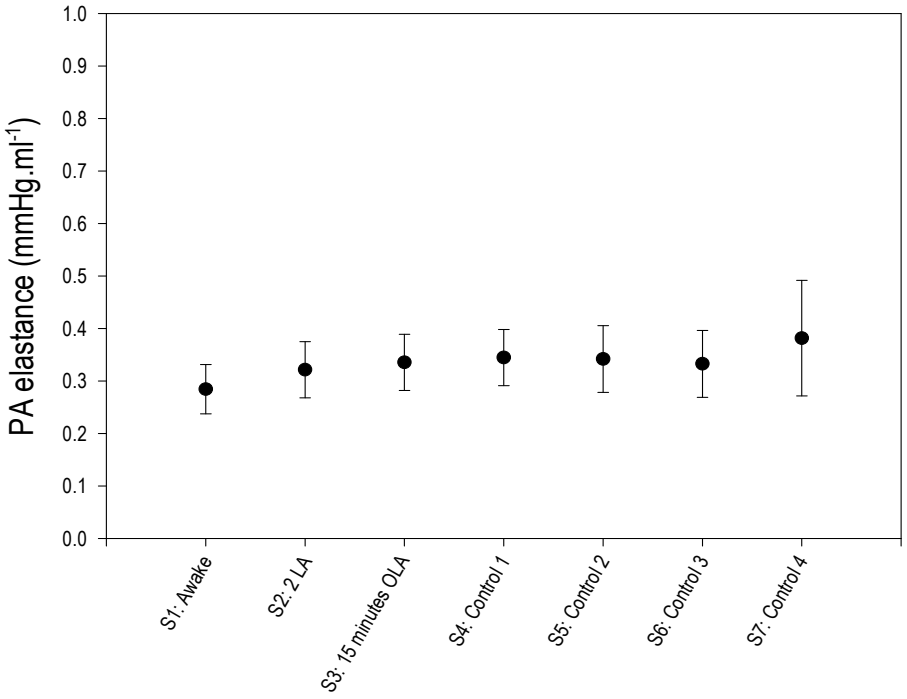


Figure 3.4.1.15 PA elastance, Control group
S7 > S1,2,3 S1< S4,5,6,7

Note that the scale of the PA elastance ranges from 0 to 1 mm Hg.ml^{-1}. The normal RV end-systolic elastance is approximately 1.7 to 2 mm Hg.ml^{-1}. Therefore, PA elastance would have to rise to 1 mm Hg.ml^{-1} before Ea/Ees approaches 0.5.

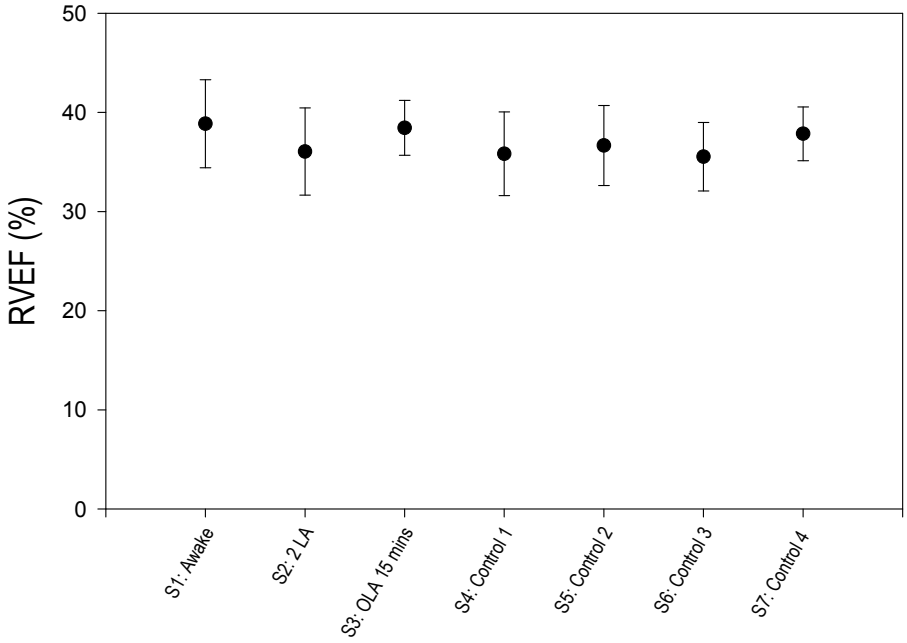


Figure 3.4.1.16 RVEF, Control group

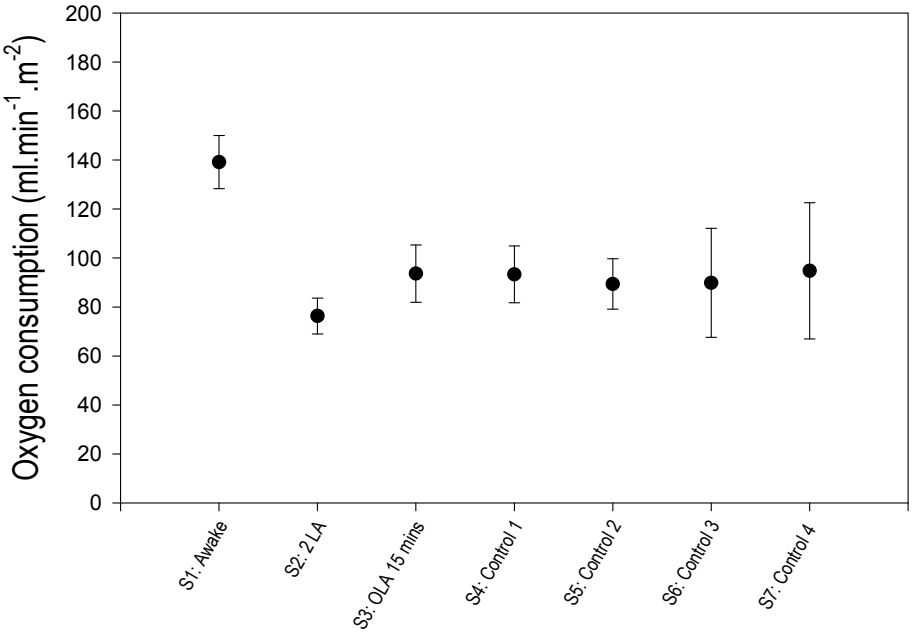


Figure 3.4.1.17 Oxygen consumption, Control group
S1 < S2,3,4,5,6,7

3.4.2 Dobutamine group

Description of steps in patients administered dobutamine	Label
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA
15 minutes after commencing one lung ventilation	S3: OLA 15 mins
5 minutes after an infusion of dobutamine 3 ug.kg^{-1}.min^{-1} was commenced	S4: Dobutamine 3
5 minutes after an infusion of dobutamine 5 ug.kg^{-1}.min^{-1} was commenced	S5: Dobutamine 5
5 minutes after an infusion of dobutamine 7 ug.kg^{-1}.min-1 was commenced	S6: Dobutamine 7

Table 3.4.2.1 The sequence of the steps and the abbreviations used in the dobutamine group graphs.

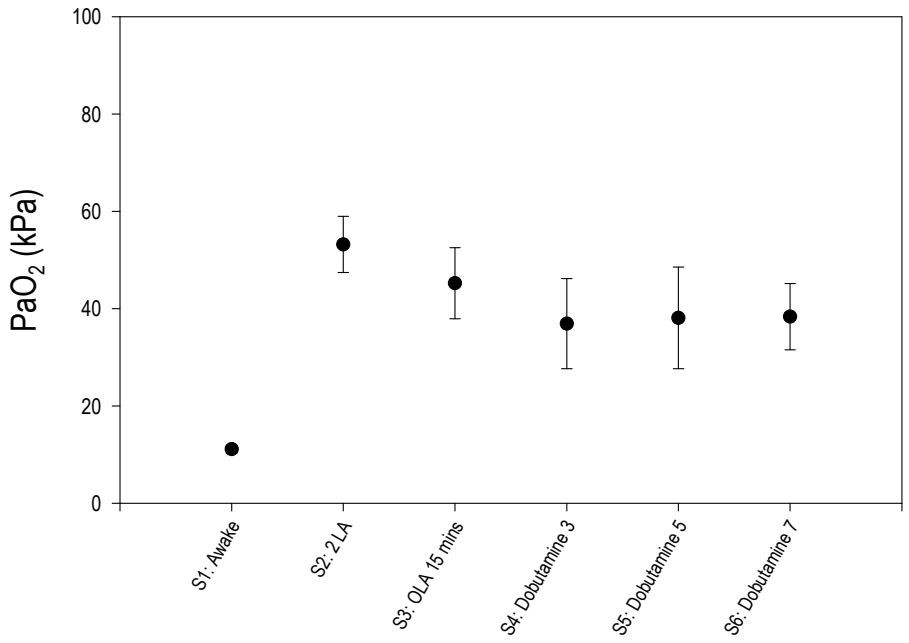


Figure 3.4.2.1 PaO_2, Dobutamine group
S1<S2,3,4,5,6 S2>3,4,5,6

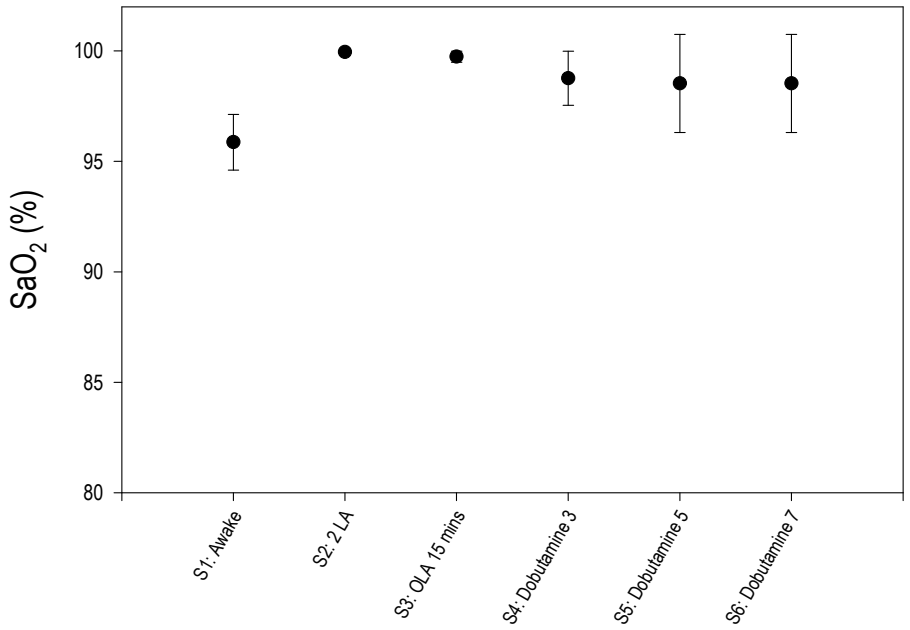


Figure 3.4.2.2 SaO_2, Dobutamine group
S1 < S2,3,4,5,6

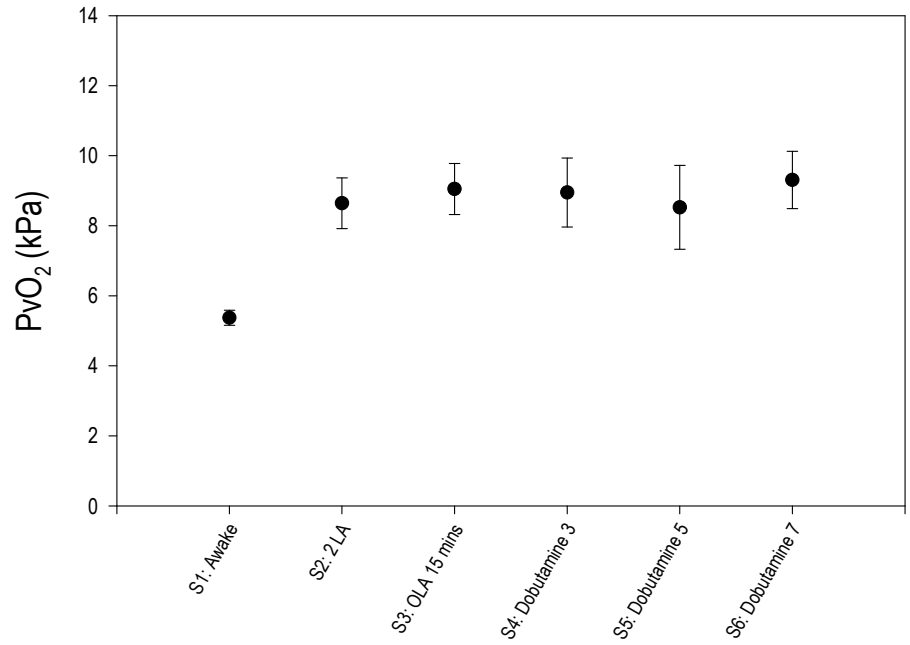


Figure 3.4.2.3 PvO_2, Dobutamine group
S1 < S2,3,4,5,6

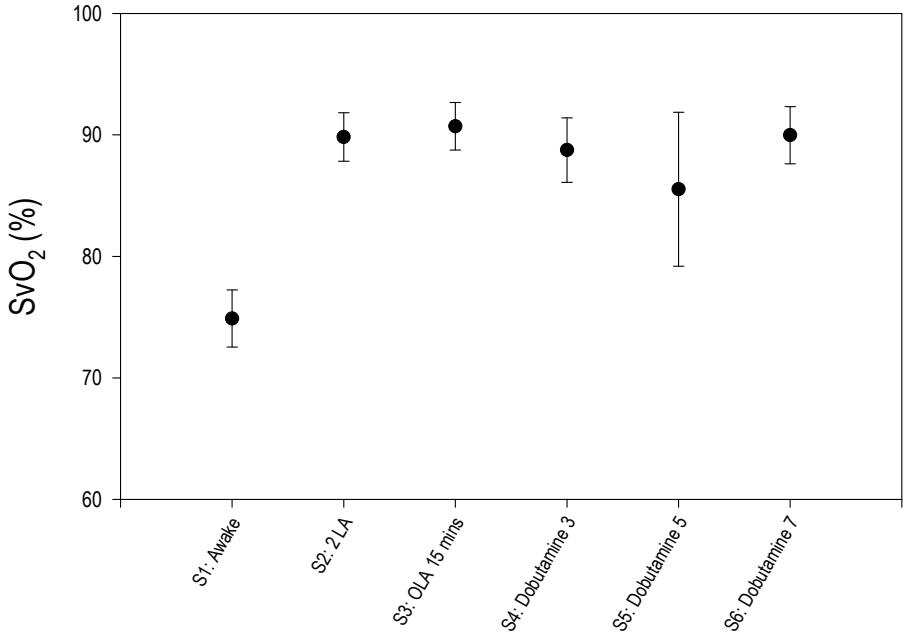


Figure 3.4.2.4 SvO_2, Dobutamine group
S1 < S2,3,4,5,6

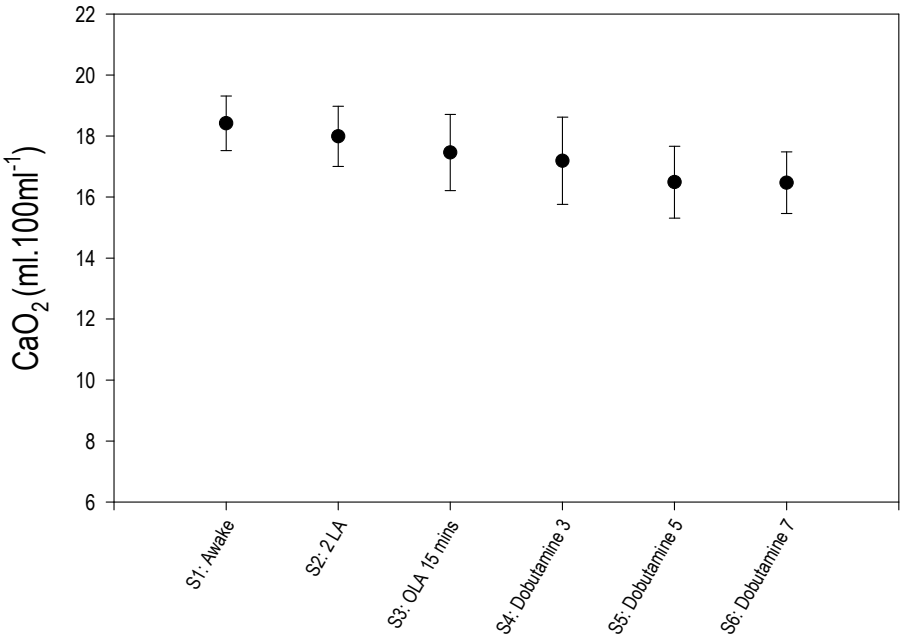


Figure 3.4.2.5 CaO_2, Dobutamine group
S1 > S5,6

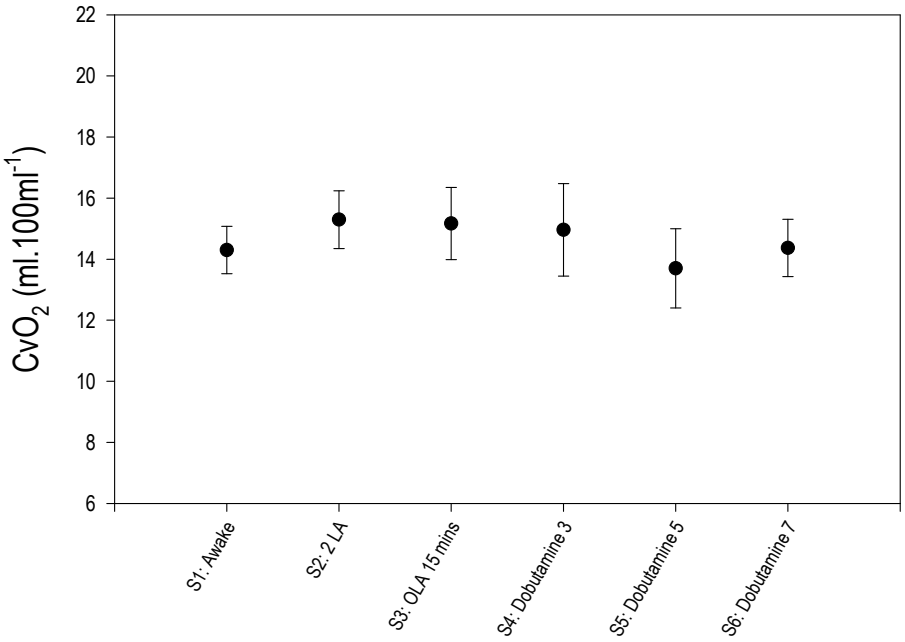


Figure 3.4.2.6 CvO_2, Dobutamine group

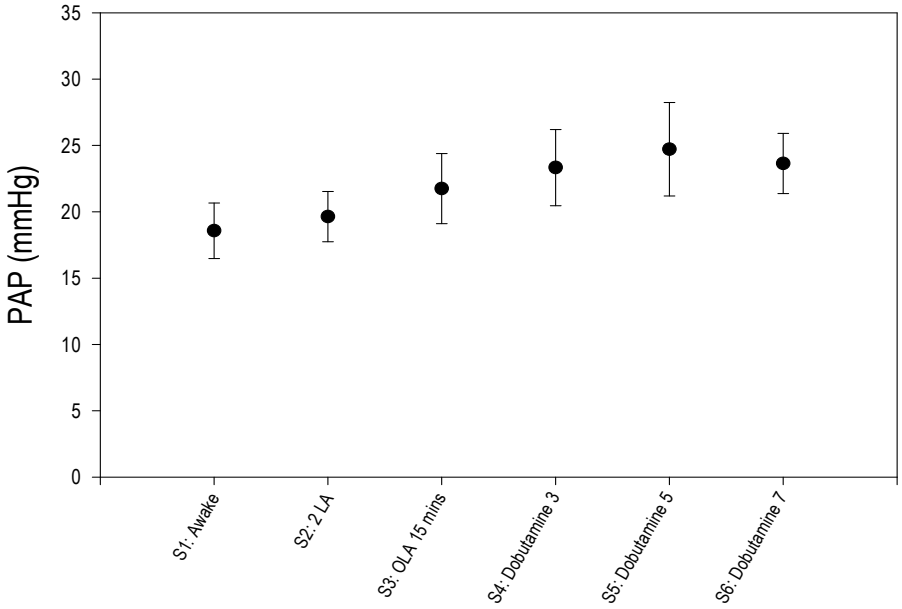


Figure 3.4.2.7 PAP, Dobutamine group
S5 > S1,2 S6 > S1,2

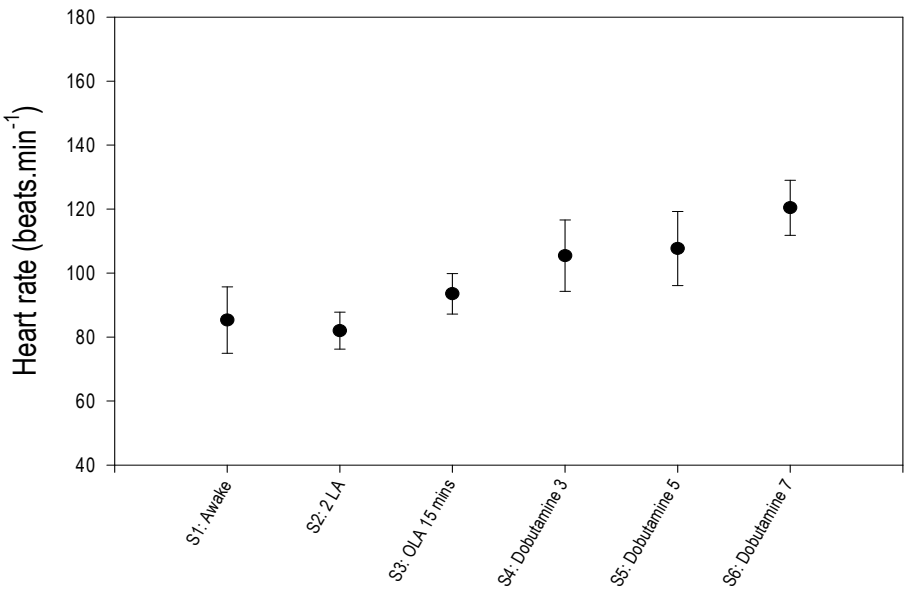


Figure 3.4.2.8 Heart rate, Dobutamine group
S6 > S1,2,3 S5 > S1,2,3 S4 > S1,2 S3> S1,2

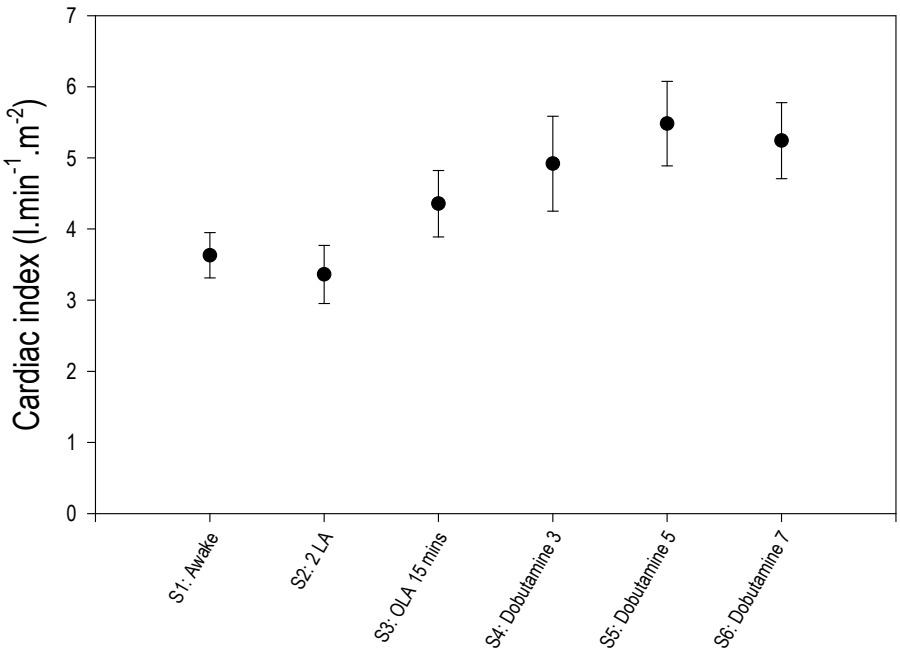


Figure 3.4.2.9 Cardiac index, Dobutamine group
S6 > S1,2,3 S5 > S1,2,3 S4 > S1,2,3 S3 >S1,2

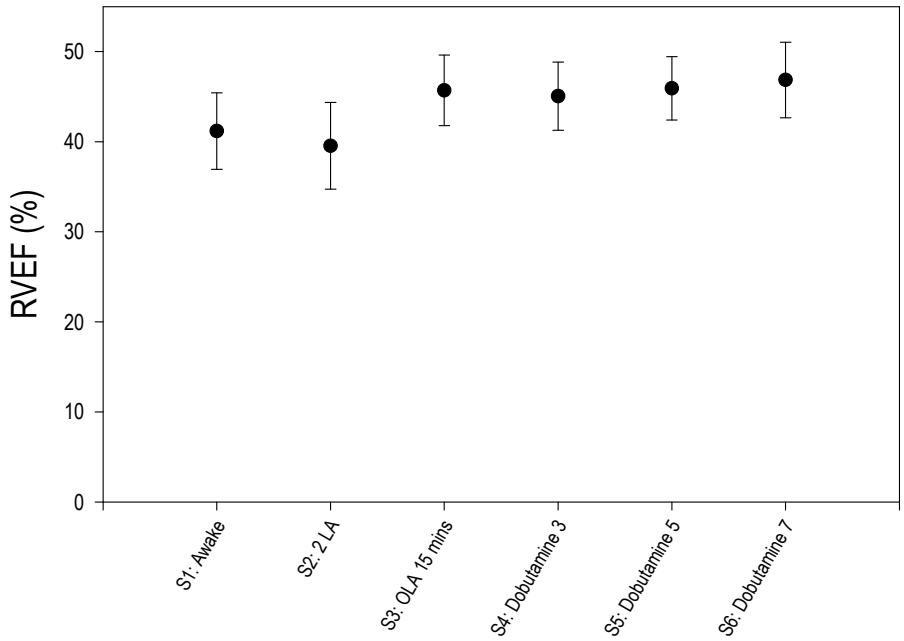


Figure 3.4.2.10 RVEF, Dobutamine group
S3,4,5,6 > S2

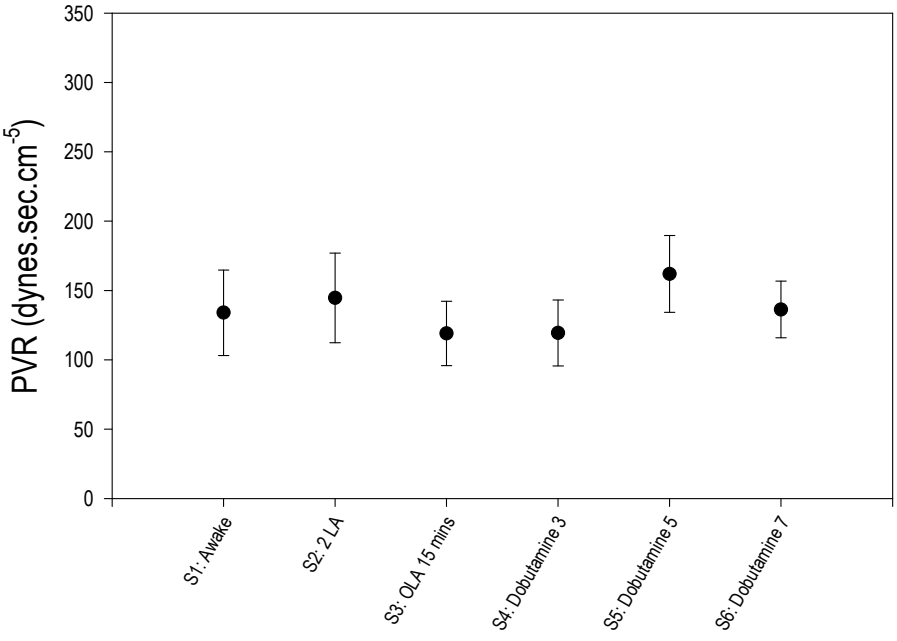


Figure 3.4.2.11 PVR, Dobutamine group
S5 > S3,4,6

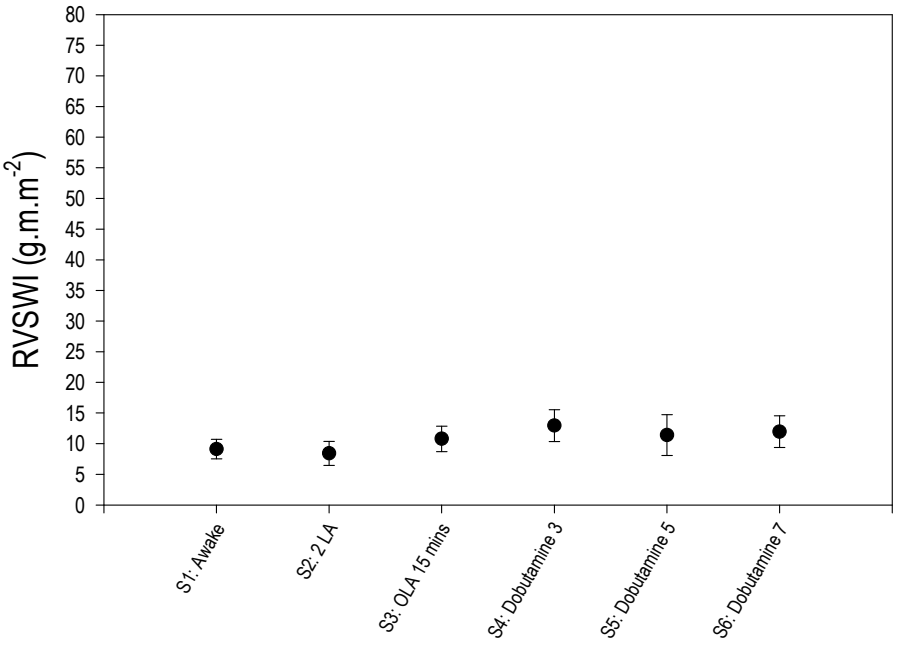


Figure 3.4.2.12 RVSWI, Dobutamine group
S4 > S1,2 S6 > S1,2

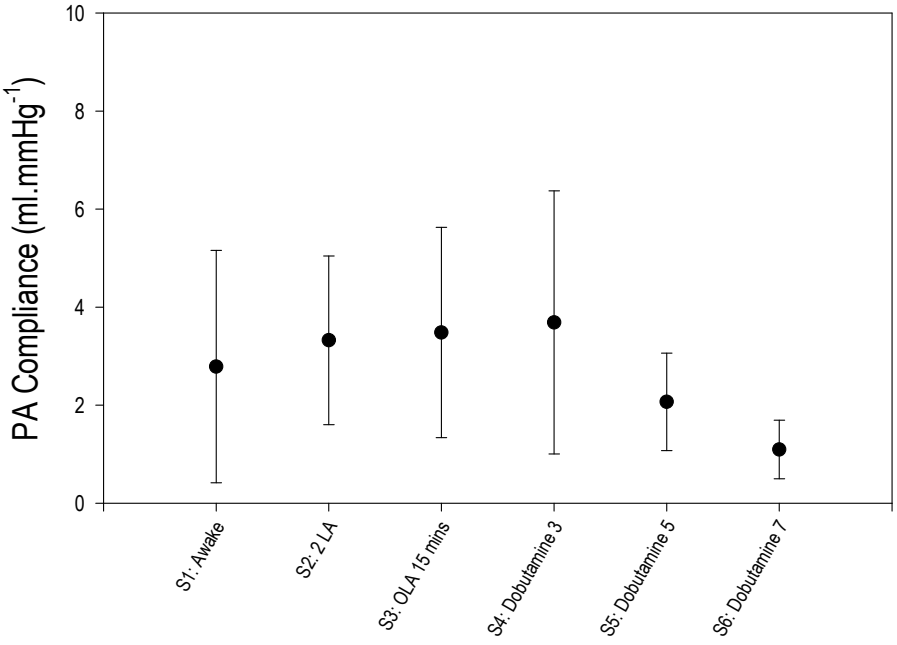


Figure 3.4.2.13 PA Compliance, Dobutamine group
S3 > S5,6

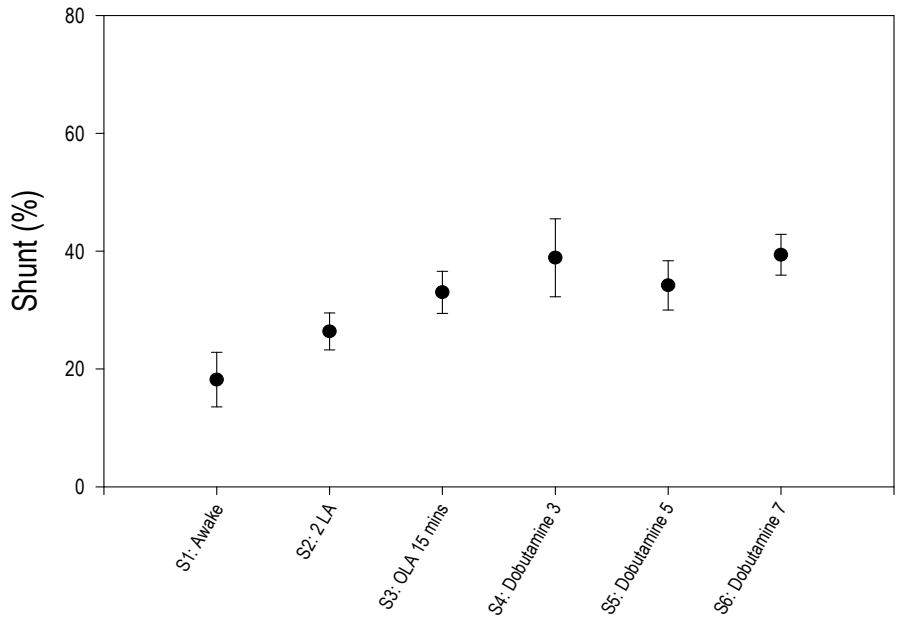


Figure 3.4.2.14 Shunt, Dobutamine group
S1 < S2,3,4,5,6 S2 < S2,3,4,5,6

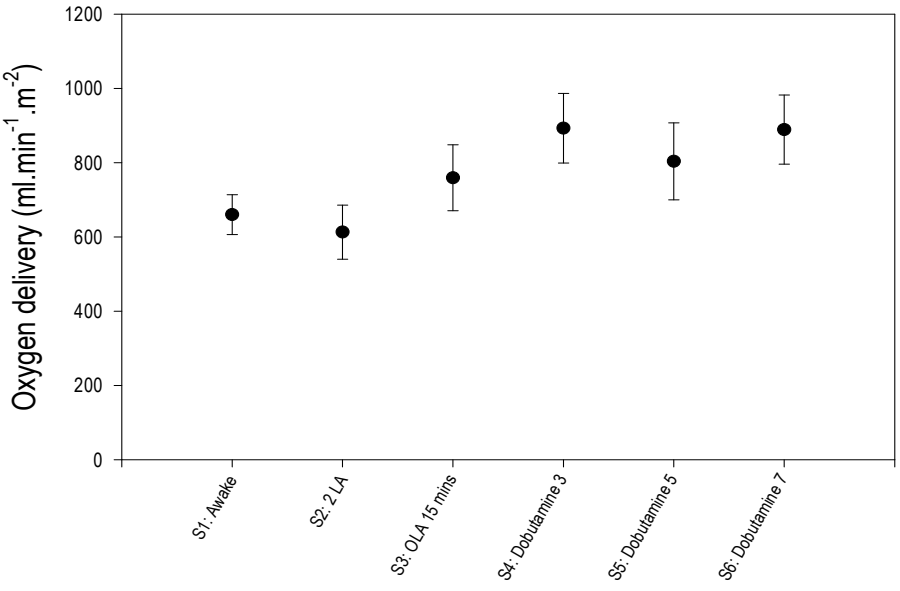


Figure 3.4.2.15 Oxygen delivery, Dobutamine group
S6 > S1,2,3 S5 > S1,2 S4 > S1,2,3

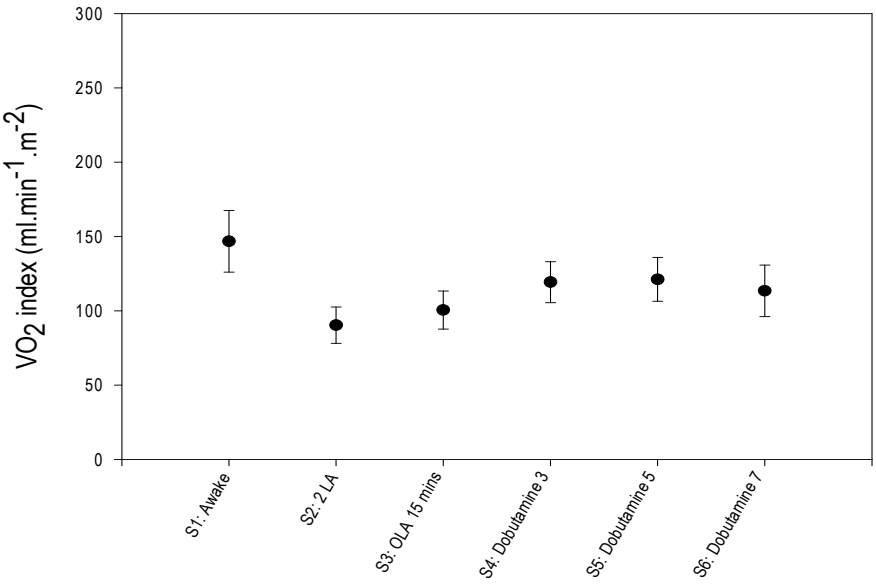


Figure 3.4.2.16 Oxygen consumption, Dobutamine group

S1 < S2,3,4,5,6 S2 < S1,5

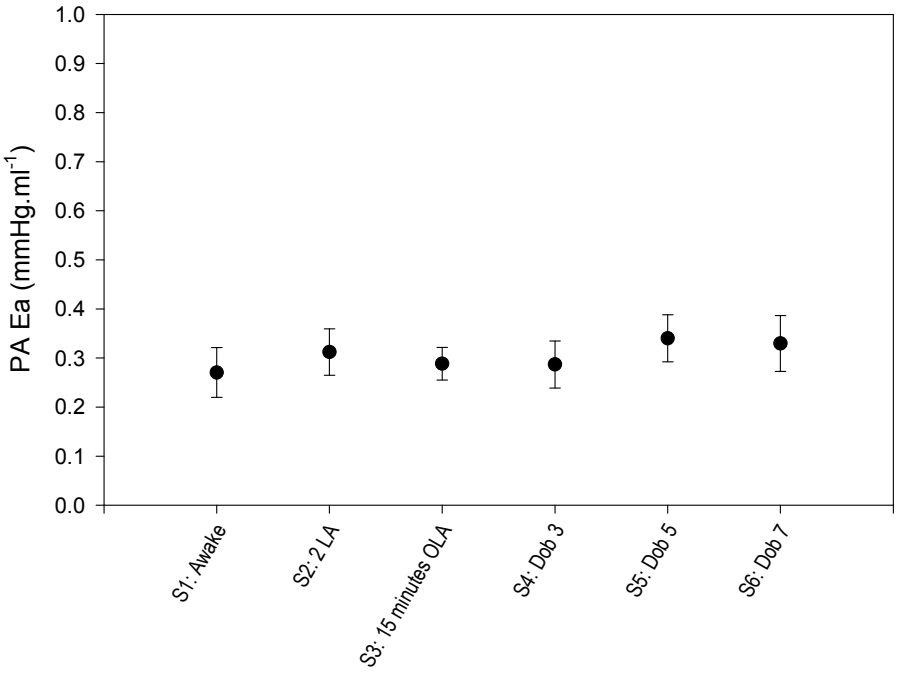


Figure 3.4.2.17 Effective PA elastance, Dobutamine group

3.4.3 PEEP group

Description of Steps in patients administered PEEP	Label
Prior to induction of anaesthesia, and before fluid pre-loading commenced	S1: Awake
In the lateral decubitus position while ventilating 2 lungs	S2: 2 LA
15 minutes after commencing one lung ventilation	S3: OLA 15 mins
10 minutes after $PEEP_5$ was applied to the dependent lung,	S4: $PEEP_5$
5 minutes after $PEEP_{10}$ was applied to the dependent lung,	S5: $PEEP_{10}$

Table 3.4.3.1 The sequence of the steps and the abbreviations used in the PEEP group graphs.

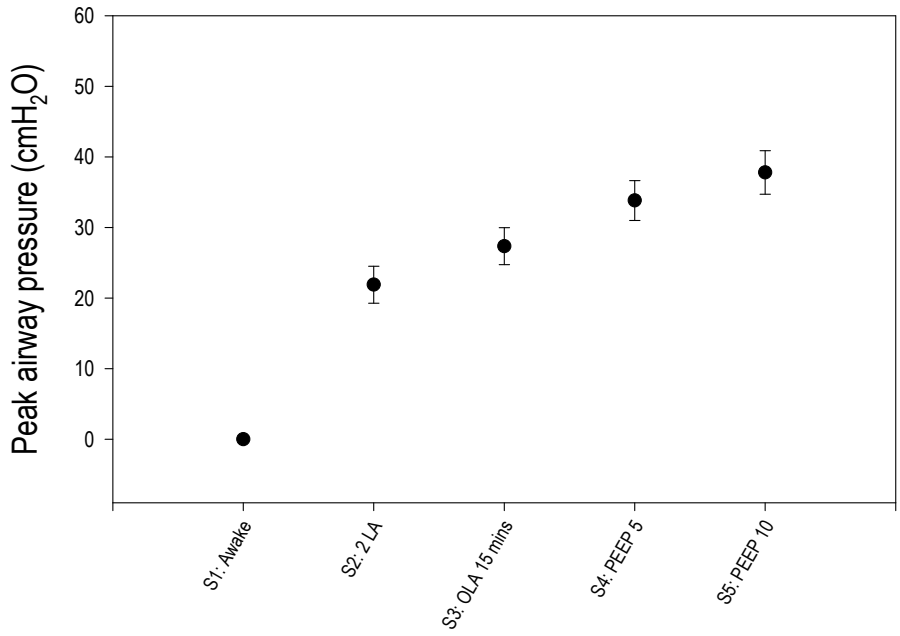


Figure 3.4.3.1 Peak airway pressure, PEEP group
S2 < S3,4,5

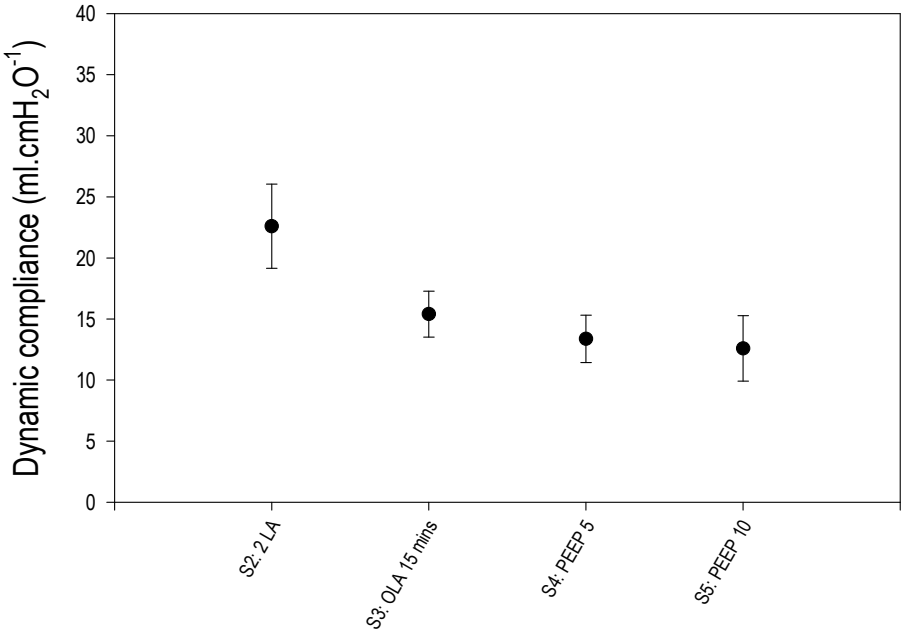


Figure 3.4.3.2 Dynamic compliance, PEEP group
S2 > S3,4,5

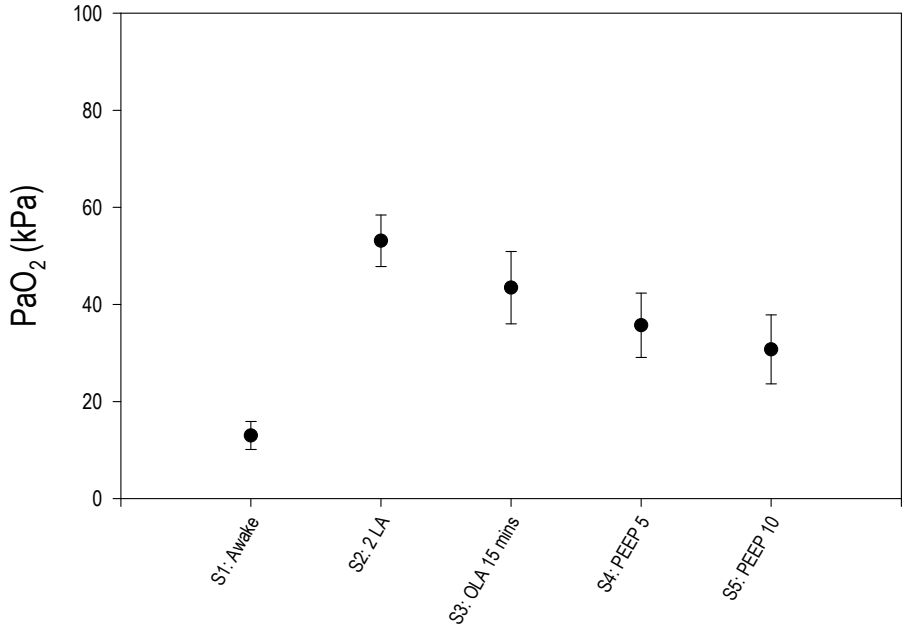


Figure 3.4.3.3 PaO_2, PEEP group
S1 < S2,3,4,5 S4 < S2 S5 < S2

3.5

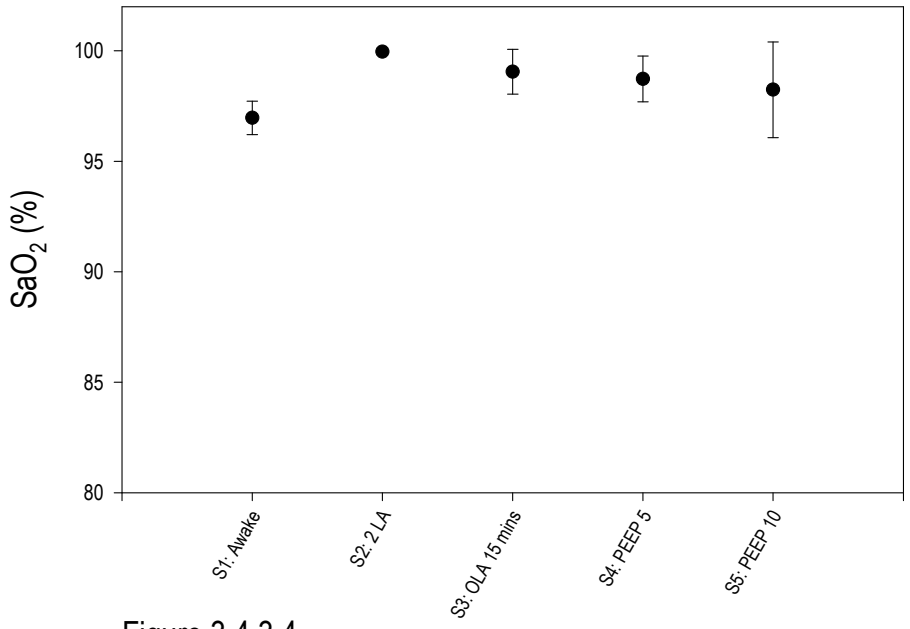


Figure 3.4.3.4
SaO_2, PEEP group

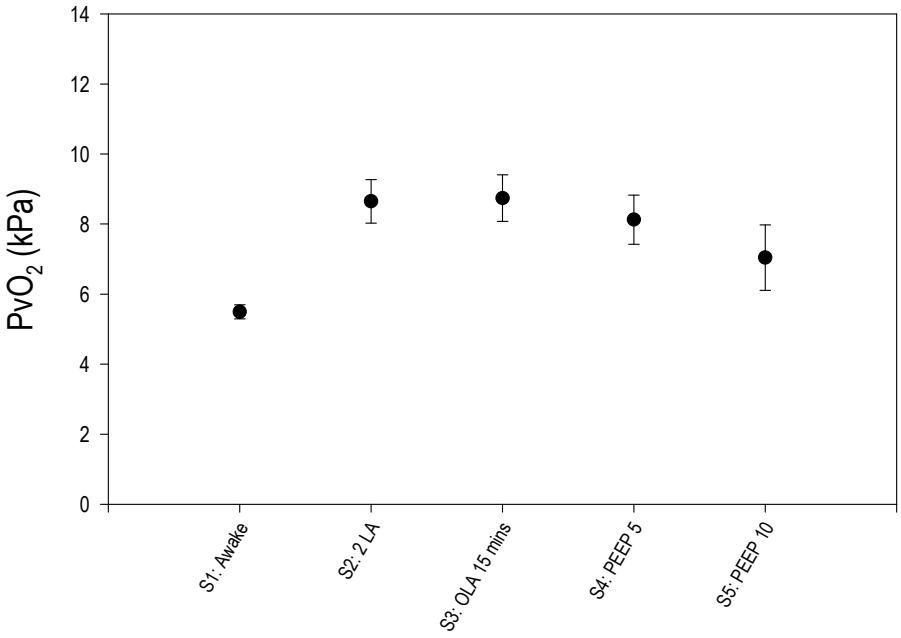


Figure 3.4.3.5 PvO_2, PEEP group
S1 < S2,3,4,5

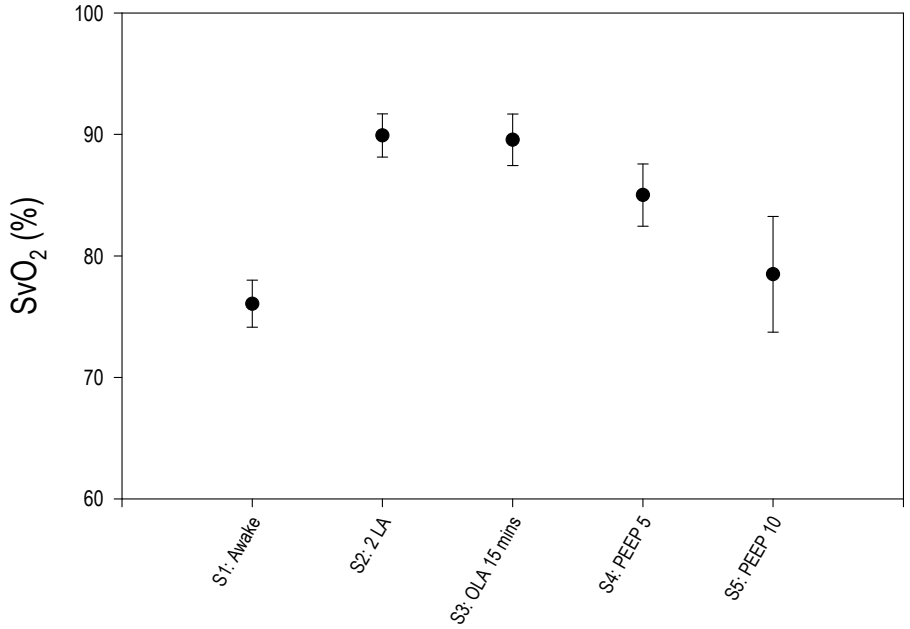


Figure 3.4.3.6 SvO_2, PEEP group
S1 < S2,3,4,5 S5 < S2,3

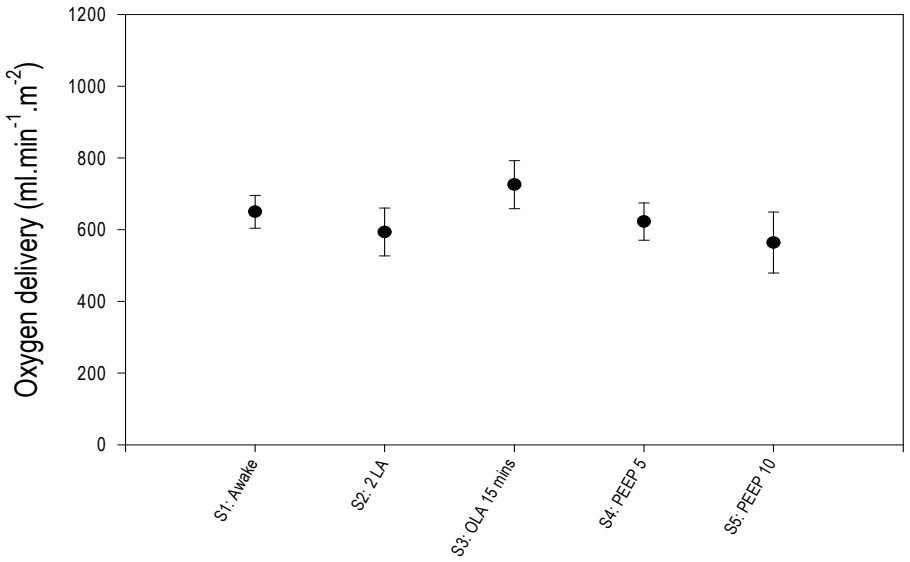


Figure 3.4.3.7 Oxygen delivery, PEEP group
S3 > S2,5

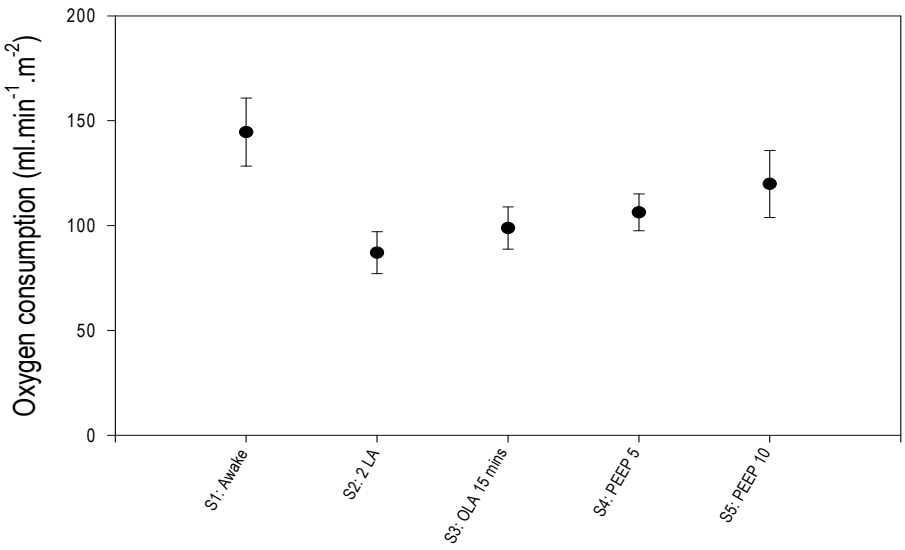


Figure 3.4.3.8 Oxygen consumption, PEEP group
S1 < S2,3,4,5

3.5 Relationships

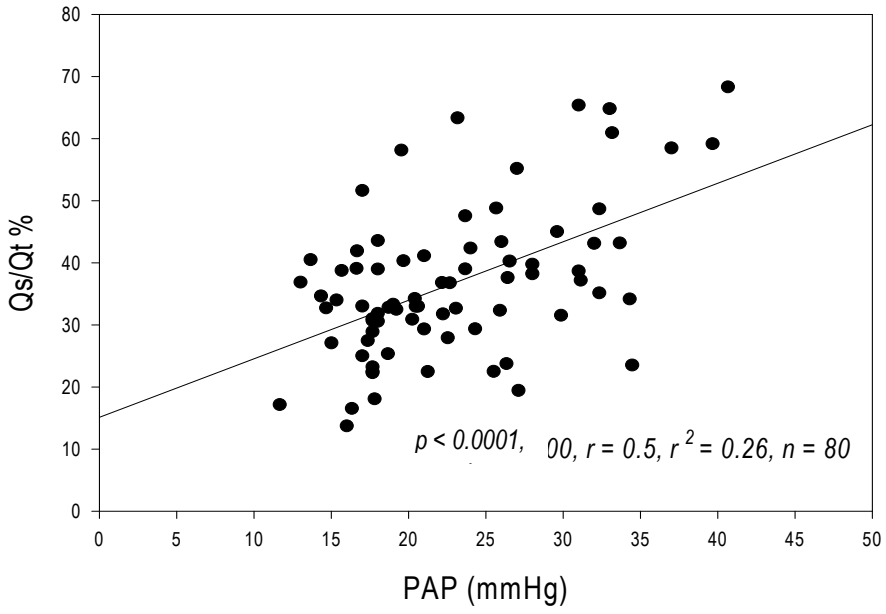


Figure 3.5.1 Relationship between PAP and Shunt
Control group, OLA steps

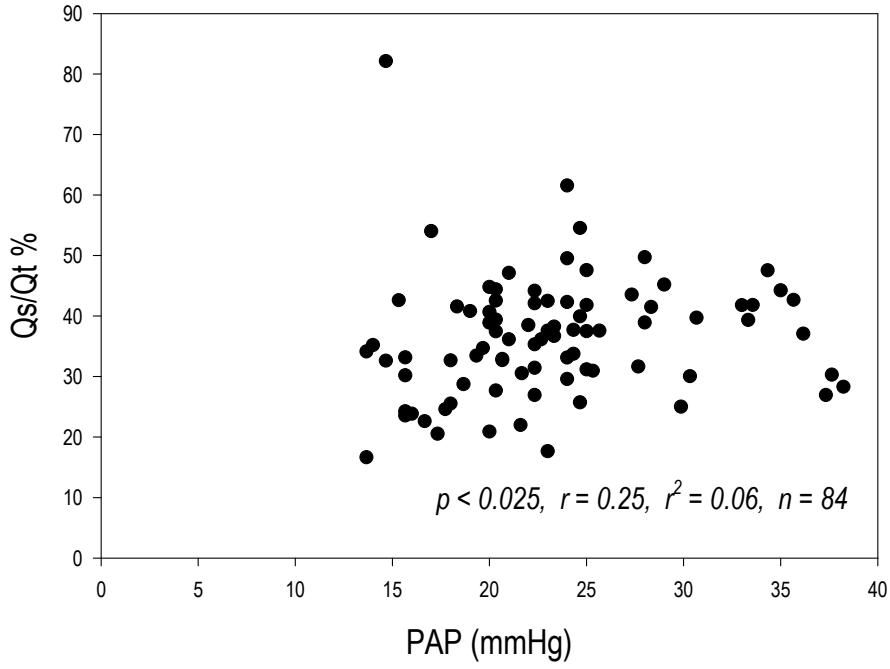


Figure 3.5.2: PAP vs. Shunt
Dobutamine group, OLA steps only

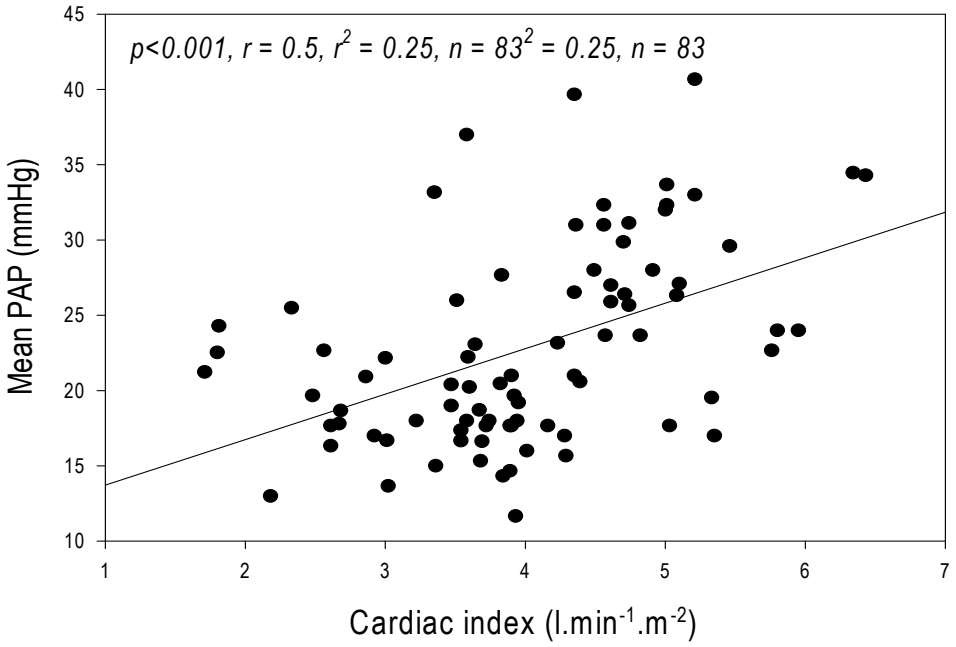


Figure 3.5.3 Relationship between cardiac index and mean PAP
Control group, OLA steps

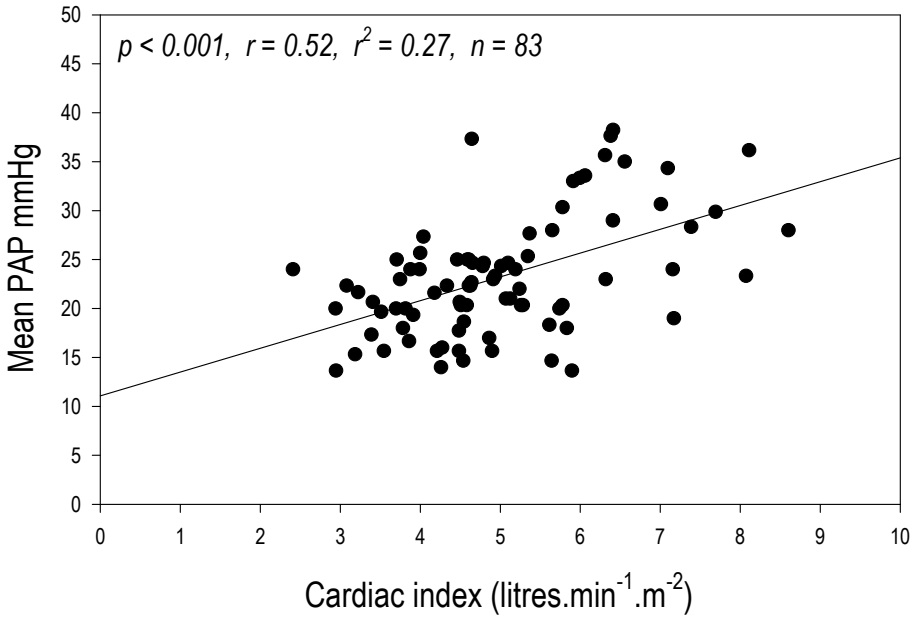


Figure 3.5.4 Relationship between cardiac index and mean PAP
Dobutamine group, OLA steps

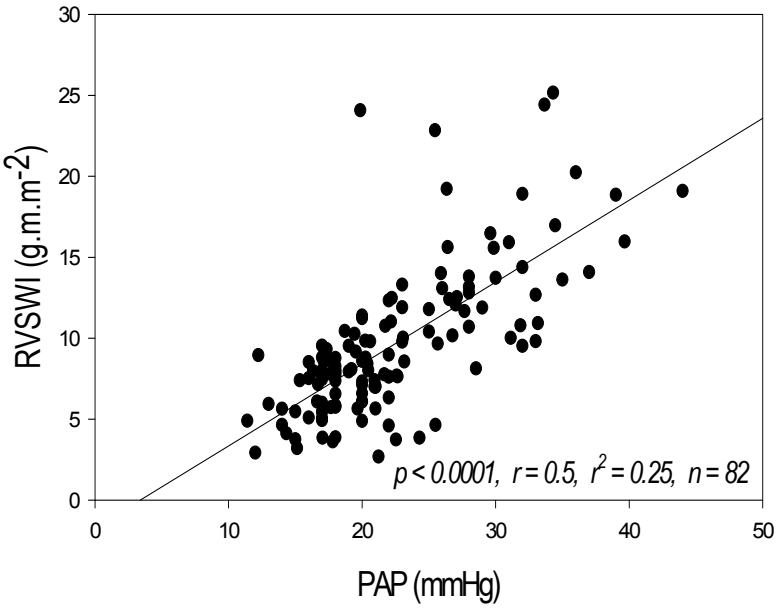


Figure 3.5.5 Relationship between PAP and RVSWI
Control group, OLA steps

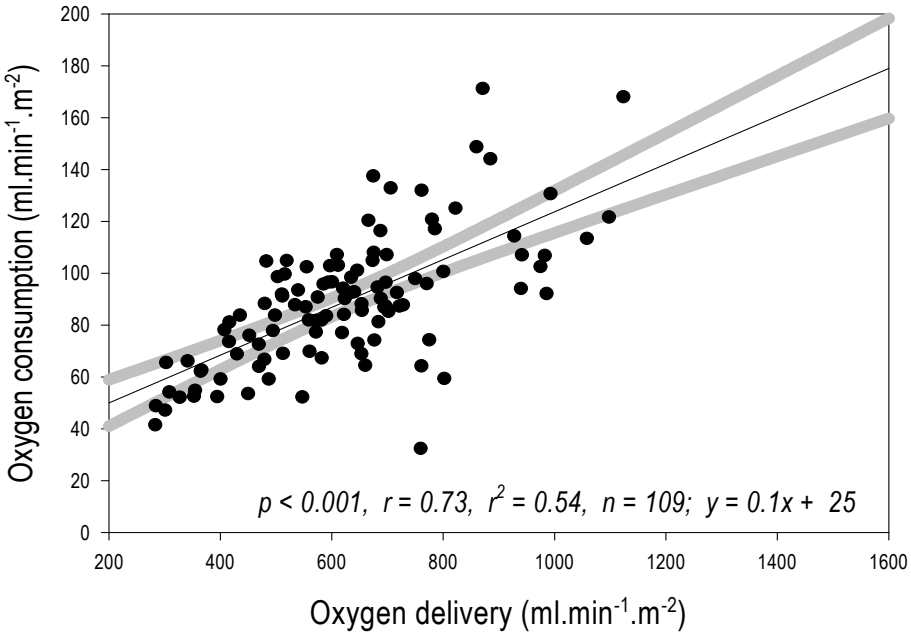


Figure 3.5.6 Oxygen delivery vs. oxygen consumption
Control Group, all anesthetised steps

The grey bars represent the 95% confidence intervals

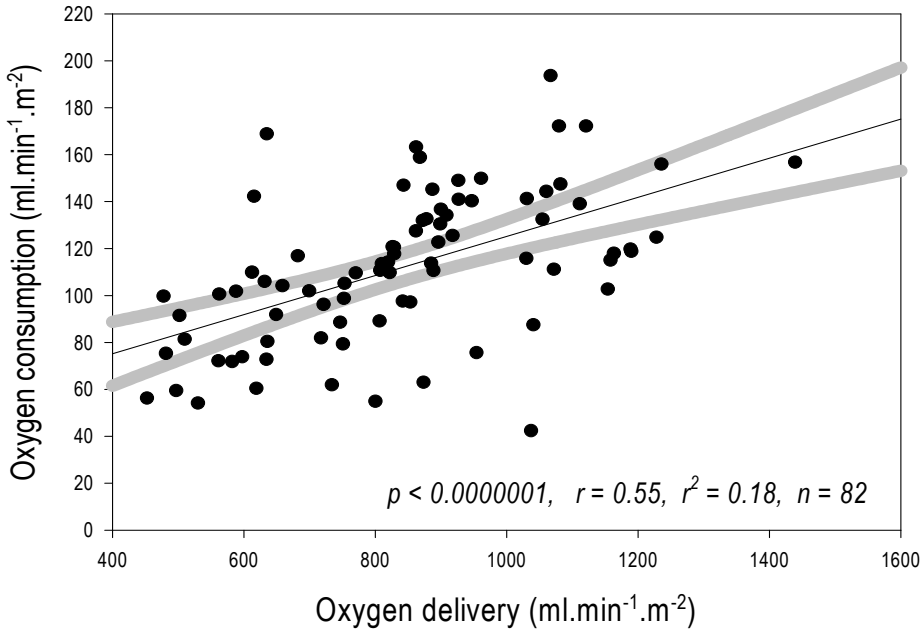


Figure 3.5.7 Relationship between oxygen delivery & oxygen consumption
Dobutamine group, all OLA steps

The grey bars represent the 95% confidence intervals

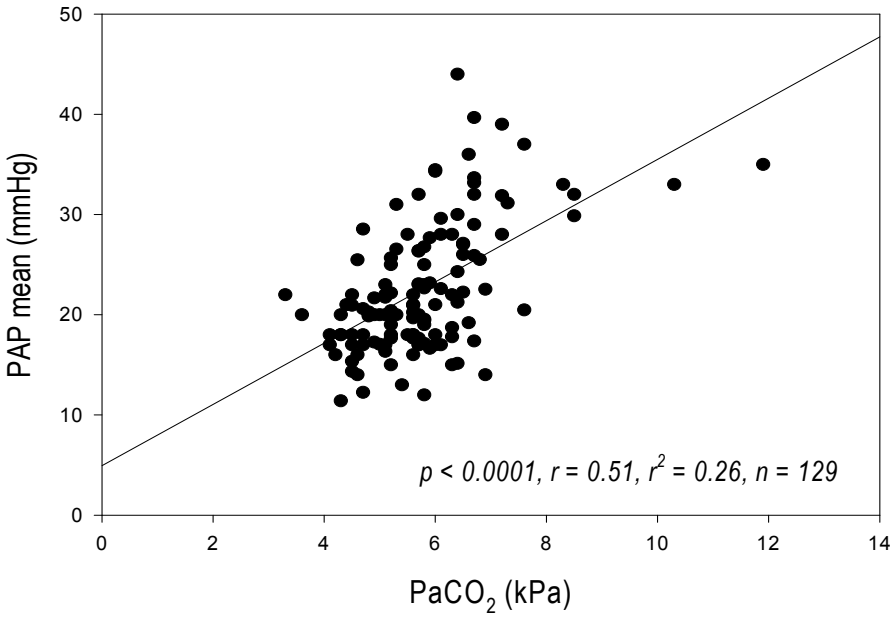


Figure 3.5.8 Relationship between $PaCO_2$ and mean PAP
Control Group, all steps

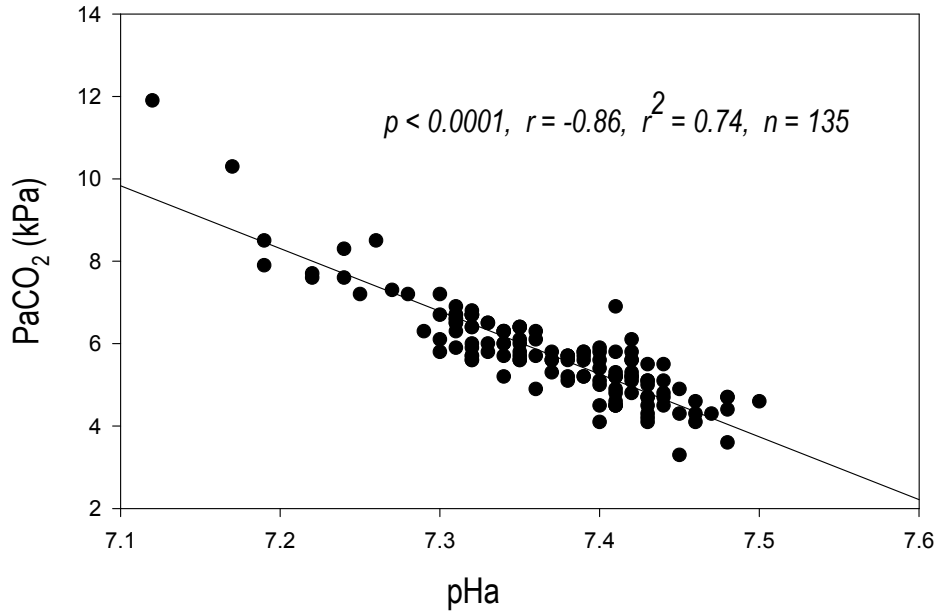


Figure 3.5.9 Relationship between $PaCO_2$ and pHa
Control group, all steps

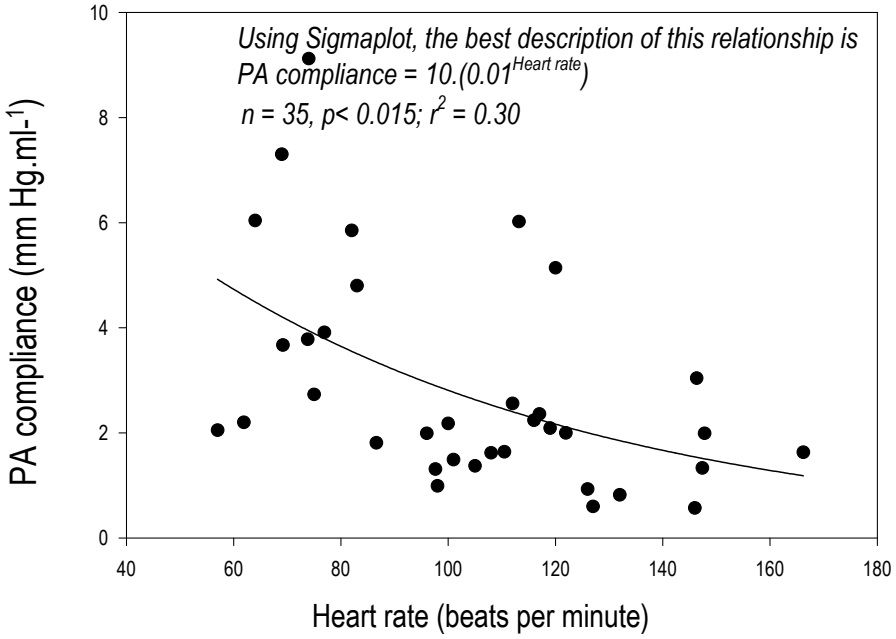


Figure 3.5.10 Relationship between heart rate and PA compliance
Dobutamine group, all OLA steps

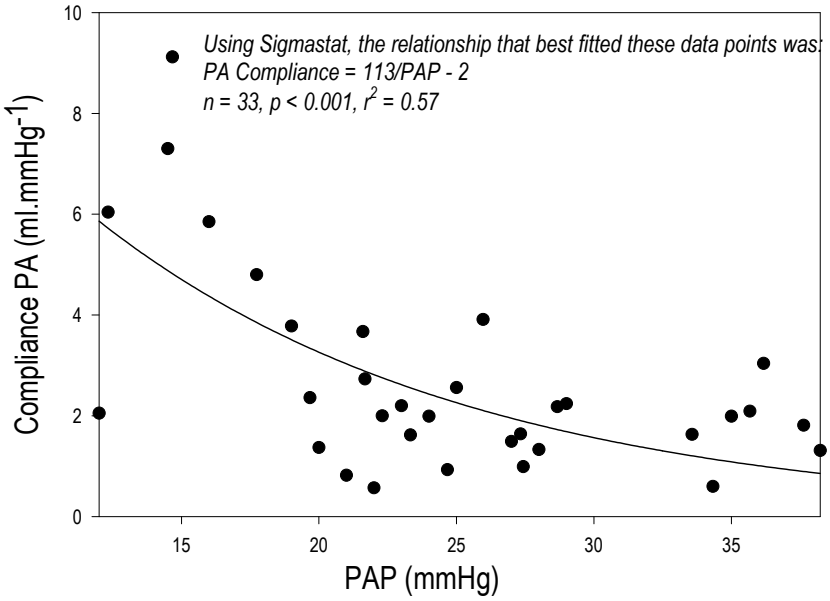


Figure 3.5.11 Relationship between PA compliance and mean PAP Dobutamine Group, all OLA steps

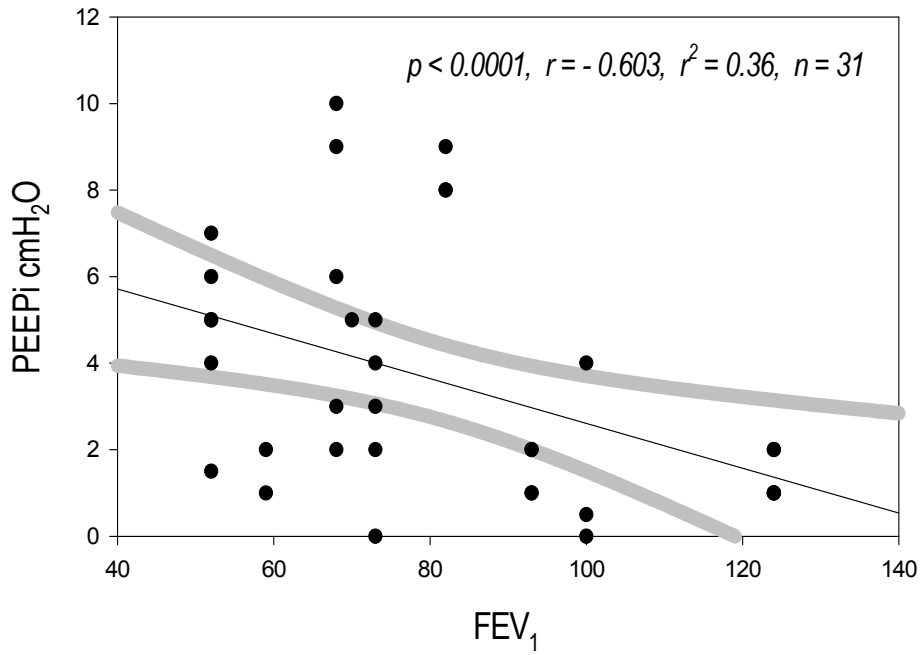


Figure 3.5.12 Relationship between FEV_1 and $PEEPi,_1$ vs. PEEPi Control group, OLA steps only

The gray bars represent the 95% confidence intervals for the regression

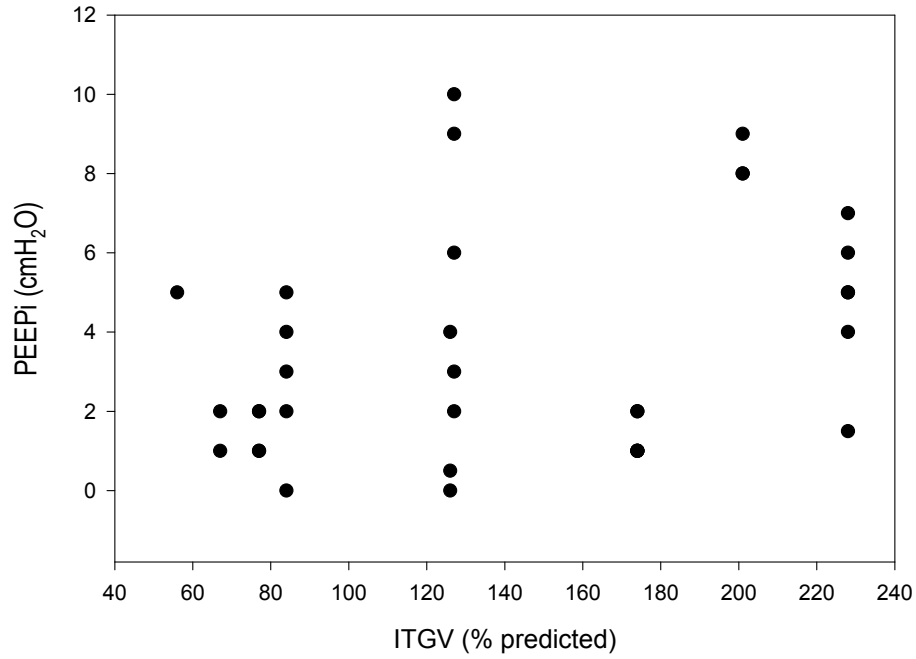


Figure 3.5.13 Relationship between ITGVplethpredicted vs PEEPi

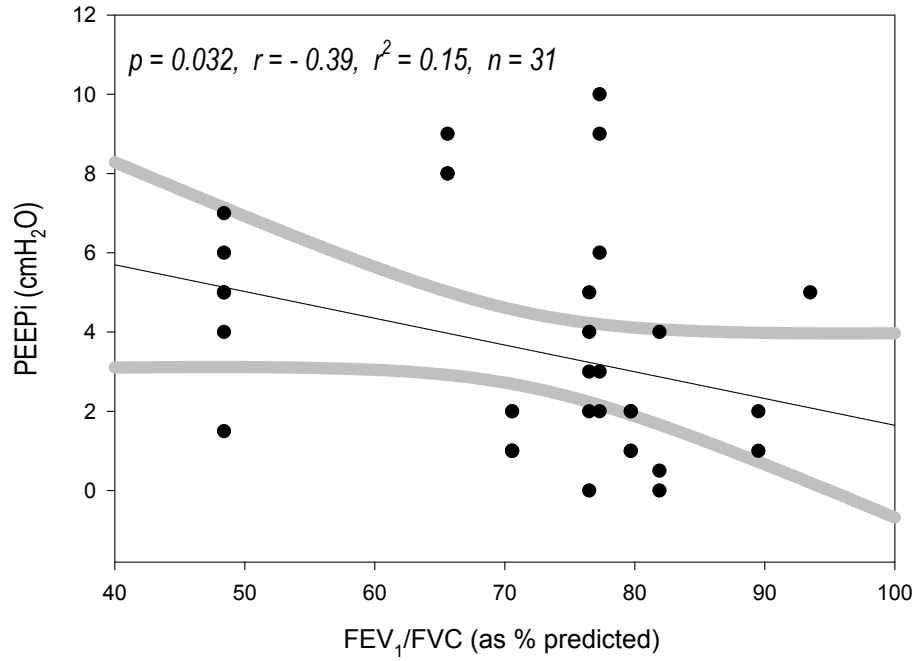


Figure 3.5.14 Relationship between FEV_1/FVC & PEEPi
Control group, OLA steps only

The grey bars represent the 95% confidence intervals

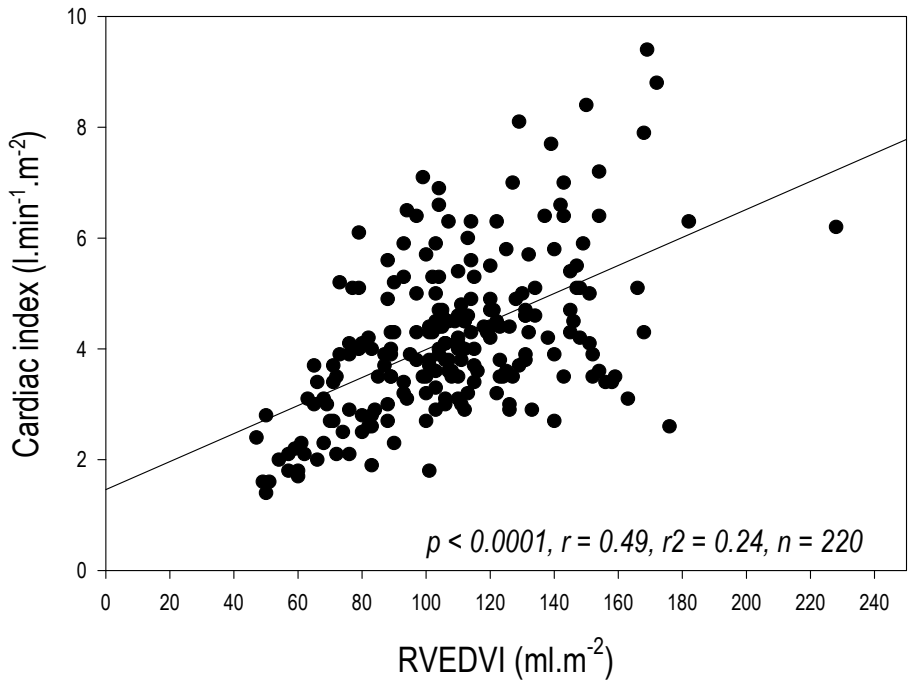


Figure 3.5.15 Relationship between RVEDVI and cardiac index
All groups and all data points

Control group OLA steps only	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
PAP (mean) and shunt	< 0.0001	0.52	0.27	80	3.5.1
PAP (mean) and PVR	< 0.0001	0.50	0.25	82	
PAP (mean) and cardiac index	< 0.001	0.56	0.32	105	3.5.3
PAP (mean) and RVSWI	< 0.0001	0.50	0.25	82	3.5.5

Table 3.5.1. Relationships between mean PAP and shunt, PVR cardiac index and RVSWI, in the control group during OLA.

Control group All anesthetised steps	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
DO_2I and VO_2I	< 0.001	0.73	0.54	109	3.5.6
DO_2I and LVSWI	< 0.0001	0.55	0.3	103	
DO_2I and heart rate	< 0.0001	0.54	0.3	104	
VO_2I and LVSWI	< 0.001	0.36	0.13	103	
VO_2I and heart rate	< 0.0001	0.39	0.15	104	

Table 3.5.2 Relationships between oxygen delivery, oxygen consumption, LVSWI and heart rate for all steps while the patient was anesthetised.

Control group All steps	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
CI and DO_2I	<0.0001	0.80	0.64	137	
CI and heart rate	<0.0001	0.54	0.3	132	
DO_2I and heart rate	<0.0001	0.46	0.2	131	
PAWP and RVEDVI	0.52	0.07	0.005	78	
CVP and RVEDVI	0.711	0.02	0.0004	83	

Table 3.5.3 Relationships between cardiac index, heart rate and delivery of oxygen for all steps in the control group.

Control group All steps	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
$PaCO_2$ and pHa	<0.0001	-0.86	0.74	135	3.5.9
$PaCO_2$ and pHv	<0.0001	-0.85	0.72	135	
$PaCO_2$ and $PvCO_2$	<0.0001	0.92	0.85	135	
$PaCO_2$ and CI	0.0011	0.278	0.08	135	
$PaCO_2$ and SI	0.70	-0.034	0.001	131	
$PaCO_2$ and heart rate	<0.0001	0.40	0.16	131	

Control group All steps	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
$PaCO_2$ and PAP	<0.0001	0.51	0.26	129	3.5.8
$PaCO_2$ and MAP	0.52	-0.06	0.0036	131	
$PaCO_2$ and PVR	<0.0001	0.33	0.11	129	
$PaCO_2$ and SVR	0.04	-0.25	0.06	70	
$PaCO_2$ and pulmonary Ro	0.63	-0.06	0.0036	69	
$PaCO_2$ and RVSWI	<0.0001	0.34	0.11	129	
$PaCO_2$ and LVSWI	0.17	0.168	0.028	70	
$PaCO_2$ and VO_2I	0.955	0.005	0.000025	132	
$PaCO_2$ and DO_2I	<0.005	0.52	0.26	132	
DO_2 and pHa	< 0.0001	0.34	0.12	132	

Table 3.5.4 Correlations of $PaCO_2$ with acid base and hemodynamic parameters for all steps in the control group.

Dobutamine group	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
PAP (mean) and Shunt, OLA steps only	0.27	0.12	0.015	84	3.5.2
PAP (mean) and CI, OLA steps only	< 0.001	0.52	0.27	83	3.5.4
DO_2I and VO_2I, OLA steps only	< 0.0000001	0.55	0.18	82	3.5.7
PAP (mean) and PVR, all steps	< 0.0001	0.37	0.14	131	

Table 3.5.5 The strength of relationships between mean PAP and shunt, PVR and CI, and oxygen delivery and oxygen consumption in the dobutamine group.

Control group OLA steps only	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
PEEPi and ITGV (plethysmography) as % predicted	0.048	0.36	0.13	31	3.2.13
PEEPi and FEV_1/FVC as % predicted	0.032	- 0.39	0.15	31	3.2.14
PEEPi and FEV_1 as % predicted	< 0.0001	- 0.60	0.36	31	3.5.12

Table 3.5.6 Relationships between preoperative pulmonary function testing and PEEPi during OLA. Note that ITGV, FEV_1/FVC and FEV_1 were expressed as a percentage of predicted normal for that patient's height, weight and sex.

PEEP group	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
The decrease in MAP (%) and the preoperative ITGV during all PEEP steps	0.6	--	--	36	

Table 3.5.7 The relationship between the percentage decrease in MAP and the preoperative ITGV during all PEEP steps.

All groups All patients data	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
Shunt during OLA and preoperative Q to collapsed lung (%)	0.83	--	--	63	

Table 3.5.8 Correlation between the proportions of blood flowing to the NDL determined by preoperative V/Q scan, and the shunt during OLA. Data from all available patients and groups used.

	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
Control group OLA	<0.0001	0.983	0.97	86	
Dobutamine 3 ug.kg^{-1}.min^{-1} OLA	<0.0001	0.962	0.93	19	
Dobutamine 5 ug.kg^{-1}.min^{-1} OLA	<0.0001	0.891	0.79	16	
Dobutamine 7 ug.kg^{-1}.min^{-1} OLA	<0.0001	0.966	0.93	25	

Table 3.5.9 The relationship between calculated CaO_2 and CaO_2 predicted by the Kelman, Nunn et al. equation for the control and dobutamine groups during OLA.

All patients in study	p value	Correlation coefficient, r	r^2	Number of data pairs	Figure
PAP (mean) while subjects were awake and preoperative VO_2 max	0.062	- 0.31	0.10	36	3.5.7

Table 3.5.10 Correlation between mean PAP while subjects were awake and preoperative VO_2max. Analysis used data for all patients in the study.

Control group: r^2		
	□	SD.
S1: Awake	0.92	0.05
S2: Two-lung Anesthesia, LDP	0.78	0.21
S3: After 15 minutes of OLA	0.75	0.25
S4: OLA, Control step 1	0.83	0.15
S5: OLA, Control step 2	0.75	0.26
S6: OLA, Control step 3	0.85	0.11
S7: OLA, Control step 4	0.71	0.22

Table 3.5.11 (On previous page). The strength of the correlation (r^2) (± standard deviation) between

the actual PA diastolic curve and the exponential curve fit for the control group.

Dobutamine Group: r^2		
	□	SD.
S1: Awake	0.91	0.09
S2: Two-lung Anesthesia	0.84	0.06
S3: One Lung Anesthesia	0.87	0.09
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	0.81	0.19
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	0.90	0.11
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	0.91	0.07

Table 3.5.12 The strength of the correlation (r^2) (standard deviation) between the actual PA diastolic curve and the exponential curve fit for the dobutamine group.

PEEP Group: r^2		
	□	SD.
S1: Awake	0.80	0.22
S2: Two-lung Anesthesia, LDP	0.81	0.14
S3: After 15 minutes of OLA	0.66	0.21
S4: OLA, DL $PEEP_5$	0.86	0.11
S5: OLA, DL $PEEP_{10}$	0.97	0

Table 3.5.13 The strength of the correlation (r^2) (standard deviation) between the actual PA diastolic curve and the exponential curve fit for the PEEP group.

3.6 The natural frequency and damping coefficients of transducer - catheter systems

Subject	Systemic		Pulmonary	
	Frequency Response Hz	Damping coefficient	Frequency Response Hz	Damping factor
A	19.4	0.27	7.65	0.5
B	15.95	0.21	9.45	0.37
C	25.2	0.17	8.88	0.37
D	47.1	0.11	14.2	0.36
E	25.0	0.2	13.1	0.26
F	28.7	0.4	10.0	0.4
G	22.0	0.53	8.25	0.4
H	16.7	0.21	9.82	0.38
I	50.7	0.28	14.3	0.48
J	33.59	0.32	10.11	0.38
Mean (SD.)	28.4 (12.0)	0.27 (0.12)	10.6 (2.4)	0.39 (0.07)

Table 3.6.1 Data of the natural frequency and damping coefficients for systemic and arterial catheter systems. The frequency response of the arterial catheter system is higher than that of the pulmonary arterial system ($p = <0.0002$).

3.7 The venous - arterial carbon dioxide tension difference

Control Group: $PvCO_2$-$PaCO_2$ (kPa)		
Steps	□	S.D.
S1: Awake	0.7	0.5
S2: Two-lung Anesthesia, LDP	0.8	0.3
S3: After 15 minutes of OLA	0.9	0.3
S4: OLA, Control step 1	0.9	0.5
S5: OLA, Control step 2	0.7	0.5
S6: OLA, Control step 3	1.0	0.5
S7: OLA, Control step 4	0.5	0.4

Table 3.7.1 The difference between the mixed venous and arterial carbon dioxide tensions at each measurement step for the control group.

Dobutamine Group: $PvCO_2$-$PaCO_2$ (kPa)		
Steps	□	S.D.
S1: Awake	0.6	0.4
S2: Two-lung Anesthesia	0.6	0.5
S3: One Lung Anesthesia	0.6	0.5
S4: OLA & Dobutamine 3 $ug.kg^{-1}.min^{-1}$	0.7	0.5
S5: OLA & Dobutamine 5 $ug.kg^{-1}.min^{-1}$	0.6	0.4
S6: OLA & Dobutamine 7 $ug.kg^{-1}.min^{-1}$	0.8	0.6

Table 3.7.2 The difference between the mixed venous and arterial carbon dioxide tensions at each measurement step for the dobutamine group.

PEEP Group: $PvCO_2$-$PaCO_2$ (kPa)		
Steps	□	S.D.
S1: Awake	0.7	0.4
S2: Two-lung Anesthesia, LDP	0.9	0.3
S3: After 15 minutes of OLA	0.7	0.4
S4: OLA, DL PEEP5	0.8	0.6
S5: OLA, DL PEEP10	0.8	0.4

Table 3.7.3 The difference between the mixed venous and arterial carbon dioxide tensions at each measurement step for the PEEP group.

4. Discussion

The following sequence is used to discuss the hypothesis relevant to each of the groups in turn. The discussion of each group begins by studying the opposition to pulmonary flow and the effects thereof on RV performance during OLA. Thereafter, the relationship of oxygen consumption to oxygen delivery and the effects of this relationship on mixed venous and arterial oxygenation are considered.

4.1 Discussion of methods

4.1.1 Demographics

No differences in demographic parameters were found between the different groups. It can therefore be concluded that the randomisation of the groups was adequate. From inspection of the demographic data, it is apparent that the population studied included patients with both restrictive and obstructive disease. The high prevalence of pulmonary tuberculosis in the Western Cape Province was largely responsible for a number of the patients having restrictive disease. This is interesting, as the majority of current studies during OLA in the literature involve the study of subjects with chronic obstructive pulmonary disease (Ducros, Moutafis et al. 1999; Bardoczky, d'Hollander et al. 1998; Abe, Mashimo et al. 1998; Bardoczky, Yernault et al. 1996). It must also be noted that the population studied was a selected one, the selection being related to suitability for toleration of lung resection. Particularly, this section would have excluded patients with a predicted postoperative VO_2max of less than 10 to 15 $ml.kg^{-1}$ (Coetzee 2000; Bolliger, Jordan et al. 1995).

4.1.2 The conduct of a human study

The study of human subjects is subject to a host of interesting problems. One aspect was that many load independent and dependent indices of RV contractility could not be studied (Burger, Jockwig et al. 2001; Karunanithi, Michniewicz et al. 1992; Fourie, Coetzee et al. 1992b). Furthermore, the pulmonary vasculature could only be accessed by using a long thin catheter that often resulted in less than hi-fidelity recordings of PA pressure (Gardner 1981). On the other hand, observations made while patients are operated on provide a reliable reflection of what actually happens during pulmonary surgery. This is unlike other studies where surgery was stopped before and during recording of the variables (Cohen, Eisenkraft et al. 1988). The real time nature of the study also meant that not all the planned steps could be conducted in a particular patient. The decreasing numbers of patients observed as steps progressed attests to this problem. The reasons for the drop-out of subjects were:

- The procedure finished more quickly than expected,
- Massive hemorrhage occurred due to tears of the pulmonary artery in 3 cases where extensive fibrosis secondary to tuberculosis was present,
- The DLT could not be correctly placed, was moved out of position by surgical manipulation or its position could not be confirmed and,
- Technical problems resulted in data from part or complete patient studies being lost on four occasions.

Recruitment of subjects was slower than expected. Patients who declined to be included or expressed reservations had their wishes respected. Other patients did not fulfil the inclusion criteria because of the presence of co-morbid disease such as coronary artery disease, hypertension, cardiac valve lesions, sepsis and pregnancy. Inclusion of

subjects with these diseases would have influenced hemodynamics. Furthermore, a number of patients who had undergone the lengthy recruitment process were not included due to lack of theatre time.

Conducting a study of this nature on animals is feasible. However, an animal study would not necessarily advance knowledge of how to improve the care of patients undergoing OLA. The presence pulmonary disease results frequently results in a decrease in blood blow to the lung to be operated on, as seen on preoperative V/Q scintigram (Table 3.1.2). In this respect, it is noteworthy that disparate results of similar manoeuvres have been observed in patients (with and without lung disease) and animals. For example, Inomata and colleagues, Cohen and colleagues and Abe and colleagues applied various amounts of PEEP to *patients* with normal preoperative lung function tests (Abe, Mashimo et al. 1998; Inomata, Nishikawa et al. 1997; Cohen, Eisenkraft et al. 1988). Alfery and colleagues studied the effect of PEEP in *dogs* during OLA (Alfery, Benumof et al. 1981). These studies came to different conclusions. The same problem applies to studies conducted to investigate the effects of an increase in oxygen delivery on arterial oxygenation both in humans (with lung disease) and in animals (without lung disease) (Russell and James 2000; Mathru, Dries et al. 1990). All things considered, the current study is a trade-off between greater clinical relevance versus the measurement of load independent indices of RV contractility and pulmonary impedance that could have been made in the laboratory.

4.1.3 Quality control: the pulmonary artery catheter during OLA

Both Benumof and Cohen highlight important considerations that apply to pulmonary artery catheters in the LDP (Benumof and Alfery 2000; Reich and Thys 1995). When inserted in the supine position, 90% of pulmonary artery catheters float into the right lung (Benumof and Alfery 2000; Reich and Thys 1995). When the patient is subsequently placed in the left LDP, the PAC will be in the NDL. These positional influences on the PAC position mean that mixed venous oxygen tensions, PAP, PAWP and cardiac output measurements could differ during two versus one lung ventilation, or in the right versus the left LDP. These considerations have been investigated. Simultaneous measurements of *cardiac output* were done using thermistors located in both the non-dependent and dependent lungs. The results indicate that measurement of cardiac output is not influenced by the PAC position during OLA in the LDP (Benumof and Alfery 2000; Reich and Thys 1995).

It is important to note that, in the current study, sampling of mixed venous blood was done after the PA catheter tip had been withdrawn into the RV. Pressure waveforms were checked before and after sampling to confirm the correct position of the catheter tip. This precaution ensured that mixed venous oxygen tension was an actual reflection of whole body oxygenation. Failure to do this could have led to two possible errors:

If the PAC tip had been located in the NDL, S□O_2 would have been decreased (Reich and Thys 1995). This decrease in S□O_2 would most likely have been the result of “stagnant blood flow”.

The PAC tip could have been located deep in the DL close to the pulmonary capillary bed. This would have resulted in “mixed venous” specimens drawn from the catheter tip being representative of alveolar capillary oxygen and carbon dioxide tensions (Shapiro, Smith et al. 1974). Even if the catheter’s tip was not located too deeply in the PA, too rapid withdrawal of blood from the catheter (reportedly at a rate of more than 3 ml per 60 seconds) may result in the gas tensions being representative of alveolar capillary blood, especially in patients ventilated with high partial pressures of oxygen (Wiedeman, Matthay et al. 1984). Withdrawing the catheter into the RV for mixed venous blood

sampling eliminated these concerns. The absence of a $P_vCO_2 - P_aCO_2$ difference is considered indicative of a sample representative of pulmonary capilliary blood (Shapiro, Smith et al. 1974). However, in the current study, at least a 0.3 kPa difference between arterial and venous carbon dioxide tensions was observed. This is in spite of the decreased metabolic rate induced by anesthesia that would tend to decrease the $P_vCO_2 - P_aCO_2$ difference. This $P_vCO_2 - P_aCO_2$ difference confirms that the potential problem of aspiration of pulmonary capillary blood was eliminated. This is an important consideration, as the venous oxygen tensions in the current study were unusually high. The abovementioned sources of error must be excluded as reasons for these high venous oxygen tensions. A further advantage of reinsertion would have been that the catheters would most likely have floated back into the lung via which the majority of blood was flowing, this being the dependent lung (Reich and Thys 1995). Thus, if the pulmonary artery catheter is in the dependent lung, it is most likely that it is in a West zone 3 region. The importance of this is that in zone 3, PAWP will accurately reflect left atrial pressure, even in the face of DL PEEP (Mark, Slaughter et al. 2000).

4.1.4 Quality control: dynamic response of transducers

Care was taken to ensure the dynamic response of the catheter-transducer systems were adequate. The arterial systems tested in the current study had a mean resonant frequency of 28.4 ± 12.0 hertz and a damping coefficient 0.27 ± 0.12. This represents an adequate frequency response (Gardner 1981). This frequency response will also ensure relatively accurate reproduction of the arterial pressures (Sykes, Vickers et al. 1994; Gardner 1981). The frequency responses in the arterial catheter-transducer system are slightly higher than those seen in other studies reporting on the characteristics of invasive arterial measuring systems in clinical practice (Gardner 1981).

Care was also taken to position the systemic, pulmonary arterial and airway pressure measurement transducers at the correct height. In the supine position, the reference point was mid-axillary level. In the LDP, the reference point used was the mid-thoracic height; this usually coincided with the lower horizontal border of the sternum. Adopting a similar reference point was especially important as pulmonary arterial, wedge, central venous and airway pressures are sensitive to small changes in their transducer position.

4.1.5 Quality control: the measurement of impedance

Impedance was estimated using Equation 1.4.4.12 by assuming that the PA pressure diastolic decay is a monoexponential function described by the equation $P(t) = Po\ e^{-t/\tau}$ (Fourie, Coetzee et al. 1992b; Westerhof and Elzinga 1991; Laskey, Parker et al. 1990). This method has previously been used successfully both in the systemic (Westerhof and Elzinga 1991; Yin, Liu et al. 1987) and pulmonary vasculature (Fourie, Coetzee et al. 1992b) to determine elements of the Windkessel model.

In the current study, characteristic impedance (Ro) was measured using Equations 2.9.4 and 1.4.4.12. Both of these equations solve for pulmonary arterial elastance, Ea. The former uses the pressure/SV method and the latter the Windkessel method to solve for Ea. The assumption that Ea could be determined by either of these equations is based on the excellent correlations (r = 0.997) between the Windkessel and the pressure/SV method that was achieved in Fourie's doctoral study for the RV (Fourie 1989) and also by Sagawa's group (r = 0.999) for the systemic circulation (Sagawa, Maughan et al. 1988).

To solve Equation 2.9.4, the variables, stroke volume, PA pressure, systolic and diastolic times and PVR could all be directly measured in this study. This however left the problem of two unknown variables, one that was desired (Ro), and the other being the time constant of the pulmonary arterial system. The time constant was measured by employing the above assumption that the diastolic decay of the arterial pressure waveform has a monoexponential form (Westerhof and Elzinga 1991; Laskey, Parker et al. 1990). Five beats taken from a 20 second PA pressure versus time recording were analysed per patient for each step (Laskey, Parker et al. 1990). The time constant for that particular epoch was then determined by the method described in the "Results" section. The average of 5 values was taken as the time constant of the pulmonary circulation for that epoch.

This method should therefore have provided a relatively simple method of determining characteristic impedance in the human pulmonary vasculature without having to resort to the use of high fidelity catheter tip transducers. Nonetheless, data with a wide scatter was generated. This method is therefore poorly suited to determine impedance with great accuracy. The reasons for this are outlined below.

1. Liu and colleagues state that the above method of estimating the time constant is typically associated with coefficients of determination greater than 0.95 (Liu, Brin et al. 1986). In the current study, the coefficient of determination between the actual PA diastolic curves and the exponential curve fit predicted by Microsoft Excel® was good and ranged from 0.82 to 0.97 (Tables 3.5.11, 3.5.12 and 3.5.13). Nonetheless, coefficients of determination between the recorded PA diastolic pressure decline and the regression line ($P(t) = Po\ e^{-t/\tau}$) did not always approach the excellent values (0.95 to 0.99) that have been seen before in the arterial system (Liu, Brin et al. 1986). The reasons were that the frequency response of the PA catheter-transducer system was low in the current study. The mean resonant frequency was 10.6 ± 2.4 Hz with a damping coefficient of 0.39 ± 0.07. This is below the desired requirements for accurate reproduction of the PA waveform[#]. Too low a frequency response and damping coefficient can lead to ringing (resonance) around the natural frequency of the system (Mark, Slaughter et al. 2000; Sykes, Vickers et al. 1994; Schwid 1988; Gardner 1981). The result is that harmonics of the pressure trace close to the resonant frequency will be amplified. As emphasized, this was not due to negligence of the part of the investigator as great care was taken to exclude all bubbles from the system and to connect the PA catheter directly to the transducer housing without any added connecting tubing. Rather, the problem can be attributed to the physical properties of the equipment used in these human subjects. The low frequency response is most likely because of the thinness of the lumen of the PAC, its great length and the slight elasticity of the material from which it is constructed (Sykes, Vickers et al. 1994; Fourie, Badenhorst et al. 1987). It is noteworthy that the resonant frequencies and damping factors in the current study are better than those obtained in other studies with similar sized PAC's (Fourie, Badenhorst et al. 1987).

The result of the low resonant frequency was that the diastolic decline of the PA tracing recorded in Alab at 200 Hz was frequently not smooth but showed a jagged response; in contrast, the systemic arterial trace appeared smooth

[#]The best option to achieve accurate reproduction of the PA waveform is for the catheter-transducer system to have as high a resonant frequency as possible. At a natural frequency above 25 hertz, damping will have minimal effect on PA waveform and the waverform will be accurately reproduced. (Mark, Slaughter et al. 2000).

(Mark, Slaughter et al. 2000). These artefacts occurred at a frequency of close to the resonant frequency of the system (Figure 4.1.5.1). This interference would have had two effects. Firstly and most importantly, the time constant could have been less accurately recorded. Secondly, the correlations between the curve fit in Microsoft Excel® and the exponential diastolic declines where less than those recorded previously by other authors (Liu, Brin et al. 1986).

Whereas diastolic and systolic times could be measured accurately, there are 5 to 10% errors in measurement of cardiac output and stroke volume using a PAC (Mark, Slaughter et al. 2000). The calculation of Ea using the

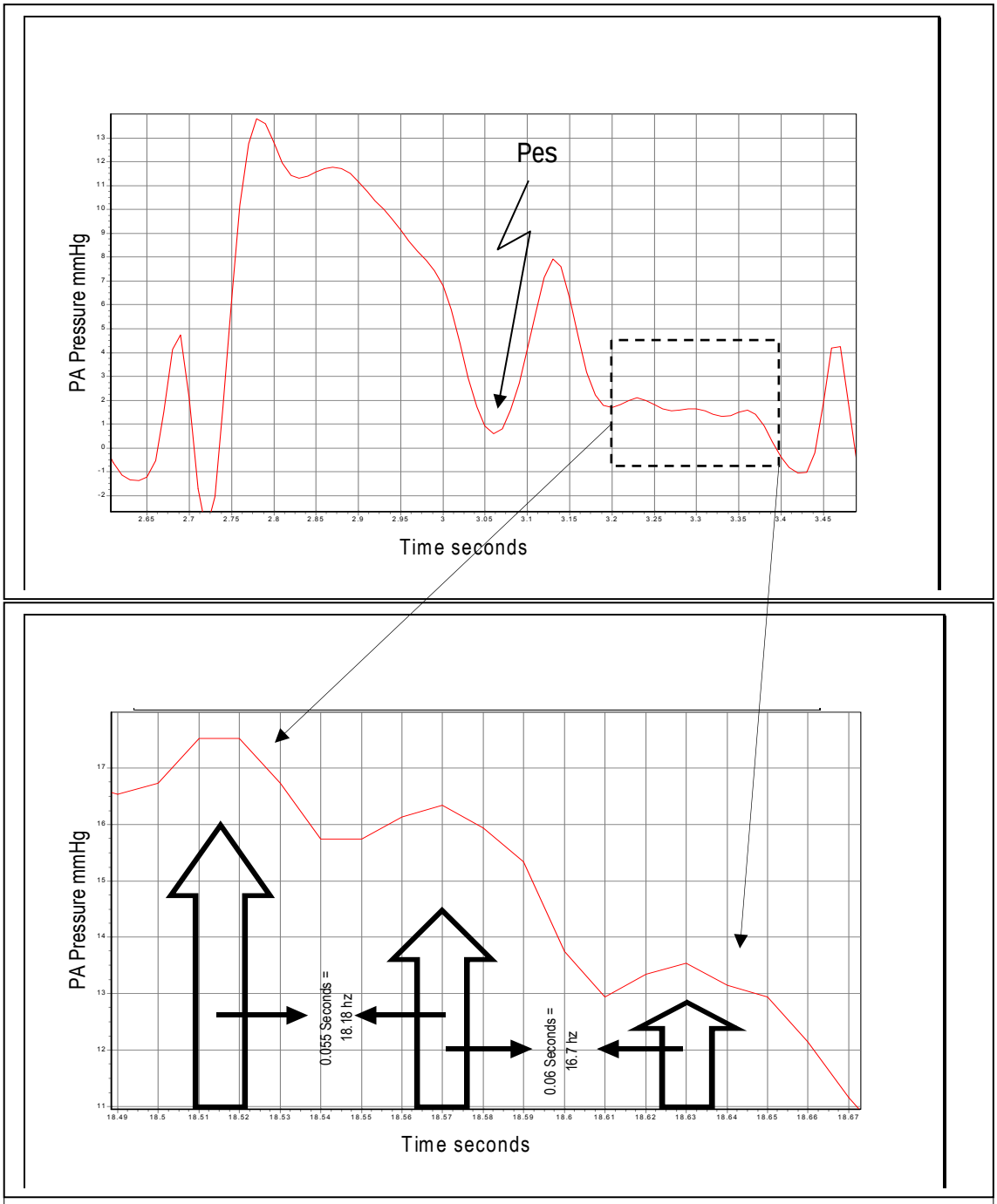


Figure 4.1.5.1 *An illustration of resonance in an underdamped PA pressure vs. time recording. In the example above, oscillation on the down slope of the PA diastolic curve occur at between 16.7 and 18.18 Hz (indicated by "hz"), close to the resonant frequency of the PA catheter – transducer system. The trough indicated by "Pes" indicates the end-systolic pressure for that beat.*

Windkessel model involves small numbers and many calculations. Small initial errors could lead to larger errors in the final calculation.

Another calculation needed to determine characteristic impedance is PVR. This is done by using the equation PVR = (PAP-LAP)/cardiac output. The method of measuring PVR in this study is a commonly used, but potentially flawed, method. The problem is that downstream pressure (LAP) is not known with accuracy. This problem of not knowing the downstream pressure also creeps into the assumptions governing the determination of pulmonary impedance using $P(t) = Po\ e^{-t/\tau}$ as the downstream pressure is ignored in this simplified formula (Liu, Brin et al. 1986). What arguments can be used in defence of the use of PAWP as a surrogate measure of downstream pressure this study? Firstly, it is likely that if the PAC had been located in the DL during OLA, it would have been subjected to zone 3 conditions. In zone 3, PAWP is an accurate reflection of LAP. Furthermore, LAP is the correct downstream pressure for zone 3 conditions. Secondly, the validity and accuracy of one-point PVR calculations have been seriously questioned (Skimming, Cassin et al. 1997). The potential error of not using a multiple pressure and flow plot is noted. In defence of not using a multiple pressure-flow plot, it is difficult to construct such a plot in humans. Albeit flawed, PVR is a commonly used clinical indicator of opposition to flow in the pulmonary circulation. Should zone 3 conditions have prevailed in the NDL (a reasonable assumption), then a pressure flow plot is not needed to determine PVR as the downstream pressure is known with reasonable accuracy.

In spite of the excellent correlation coefficients observed in their study, Yin suggests that this association is not necessarily conclusive evidence that the pressure decay declines monoexponentially (Yin, Liu et al. 1987; Liu, Brin et al. 1986). Whether this is of importance in the current study, is doubtful.

Another drawback of this method is that the calculation of the PA time constant required copying and pasting by hand of 5 pulmonary arterial diastolic tracings per patient per step from Alab into Microsoft Excel®. This is an extremely time-consuming task.

In conclusion, the physical characteristics of the PA catheter currently used in adult humans are not ideal for accurate determination of impedance. This technique for determining characteristic impedance is valid. However, only gross changes of characteristic impedance could be determined because of limitation in data collection. Possibly the method of using the area under the PA diastolic curve[#] could provide an answer to the problem of more accurate determination of characteristic impedance in human subjects using a standard PAC (Liu, Brin et al. 1986).

4.2 Control group: OLA and the opposition to pulmonary flow

The relevant part of the hypothesis to be examined in this section was that OLA increases RV afterload and thereby impairs coupling to its load. It was hypothesised that this increase in afterload would have had deleterious effects on RV performance. The parameters that were used to study the opposition to flow in the pulmonary vasculature were

[#] Liu, Brin and colleague (Liu, Brin et al. 1986), using the concept of a two element Windkessel model, developed a method of determining vascular compliance using the area under the pressure tracing rather than the waveform itself. This eliminates the problem of the waveform not being monoexponential in form. The formula that they derived is: $RC = t_d/[Ln\ (Ps - Po) - Ln(Pd - Po)]$ where t_d is the total duration of diastole, R is total vascular resistance, C is vascular compliance, Ps is the pressure at the dicrotic notch, Po is the venous pressure (or better the pressure at zero flow in the vascular bed) and Pd is the diastolic pressure. Please see the original article for the relatively simple derivation of this formula.

pulmonary arterial pressure, elastance, resistance, compliance, and characteristic impedance. It is noteworthy that mean PAP increased from 19 ± 5.1 mm Hg to a maximum of 25 ± 4.8 mm Hg during OLA. This represented a 32% rise in mean PAP observed in the current study after initiation of OLA This increase in mean PAP on initiation of OLA is greater than that observed by certain investigators (Pagel, Fu et al. 1998; Malmkvist, Fletcher et al. 1989; Malmkvist, Fletcher et al. 1989; Carlsson, Bindslev et al. 1987; Carlsson, Hedenstierna et al. 1987; Werner, Malmkvist et al. 1984) but similar to that seen previously in patients with damaged lungs (Boldt, Muller et al. 1996; Flacke, Thompson et al. 1976).

Why does pulmonary artery pressure rise during OLA? From consideration of Ohm's law, pressure may be regarded as the product of flow and resistance (Mark, Slaughter et al. 2000). In the current study, the relationship between pulmonary artery pressure and PVR demonstrated that the increase in PVR accounts for 25% of the increase in mean PAP (Table 3.5.1). This is a surprising observation as it is commonly stated that as flow and pressure increase in the pulmonary vascular bed, PVR is reduced by vasodilatation and recruitment (Domino 1997; Rodman and Voelkel 1997; Basson 1996; West 1985). In other words, as flow and pressure increase, recruitment and vasodilatation should limit the increase in pulmonary artery pressure. This should result in a decrease in PA elastance. It is apparent that the aforementioned concept does not hold true for this group of patients during OLA, as indicated by the rise in PA elastance when PA flow and pressure increase. If the relationship does not hold, it may well indicate that pulmonary vascular recruitment and dilatation are more limited in scope for these patients than is usual (Cryer, Mavroudis et al. 1990; Crouch, Lucas et al. 1987). The reason for the limited pulmonary vascular reserve is probably because the pulmonary vascular bed of patients subjected to OLA is frequently abnormal. A number of reasons for an abnormal pulmonary vascular bed might be the following:

- Similar disease processes as in the lung being operated on frequently affect the dependent lung.
- During OLA in the lateral decubitus position, lung volume decreases to a greater degree than during two-lung anesthesia (Klingstedt, Hedenstierna et al. 1990). This will lead to an increase in PVR. The consequence of a low lung volume is also an increased number of low V/Q units in the DL. This will result in DL HPV. The mechanical obstruction and vasoconstriction will both contribute to an increase in PVR (Capan, Turndorf et al. 1990).
- This decrease in lung volume will be further aggravated by DLT malpositions, secretions and blood, and absorption atelectasis due to the use of high concentrations of oxygen (Hedenstierna 1998; Krucylak, Naunheim et al. 1996).
- Excessive amounts of extrinsic or intrinsic PEEP during OLA can compress the intra-alveolar capillaries and deleteriously affect the pulmonary vascular resistance (Ducros, Moutafis et al. 1999; Inomata, Nishikawa et al. 1997; Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996).

The aforementioned processes will result in a steeper relationship between flow and pressure in the pulmonary vasculature and most likely account for the increase in pulmonary artery pressure during OLA. A problem aggravating this rise in resistance is that it is likely that flow through the DL vascular bed increased during OLA in the current study. The increase in DL flow is due to two factors peculiar to OLA:

1. Approximately 50% of the cardiac output usually flows through each lung. During OLA a significantly greater portion of the cardiac output typically courses through the vascular bed of the dependent lung.

2. The 30% increase in cardiac index observed on initiation of OLA in this and other studies (Abe, Mashimo et al. 1998; Boldt, Papsdorf et al. 1997; Cohen, Eisenkraft et al. 1988) will also aggravate the increase in PAP. The greater portion of this increase in cardiac output will flow via the DL. This will further increase DL lung flow.

If it is likely that in these patients, recruitment and dilation was exhausted, the relationship between pulmonary blood flow and pulmonary artery pressure is a straight line (Figure 1.4.2.2.3). Therefore, an increase in pulmonary blood flow would have resulted in an increase in PAP. This contention is supported by an examination of the relationship between flow (cardiac index) and mean PAP during OLA in the current study. It can be seen that the increase in flow accounts for 25% of the rise in mean PAP (Figure 3.5.3). Therefore in summary, the rise in mean PAP during OLA is due to two reasons. Firstly, the pressure versus flow curve is steeper during OLA. Secondly, there is greater flow through this vascular bed that possesses a higher resistance.

It is remarkable that in spite of the increase in PAP, no increases in PVR were measured during OLA in the control group of the current study. The explanation may again lie in considering pulmonary vascular resistance as the slope of the relationship between flow and pressure (Figure 1.4.2.2.3) (McGregor and Sniderman 1985; Mitzner 1983). Thus, the greater the damage to the pulmonary vasculature, the higher will be the PVR as reflected by a steeper gradient of the pressure versus flow relationship. In a normal lung, this relationship is such that for every litre per minute increase in cardiac index, mean PAP rises by 1 mm Hg. A higher resistance in a damaged pulmonary vascular bed will contribute to the reasons why mean PAP but not PVR increased when the cardiac output and flow to the NDL rose during OLA.

As PA pressure increases during OLA, the forces producing hypoxic vasoconstriction of the vasculature in the NDL are progressively opposed with eventual elimination of HPV at PA pressures greater than 25 mm Hg (Benumof 1991; Benumof and Wahrenbrock 1975). The strength of the relationship between increases in mean PAP and shunt fraction in this study is not strong. The increases in mean PAP account for only 26% of the increase in shunt fraction occurring during OLA (Figure 3.5.1). However, the strength of the relationship between mean PAP and shunt fraction is similar in magnitude to that described by Malmkvist and colleagues (Figure 1.7.1.2) (Malmkvist, Fletcher et al. 1989; Malmkvist, Fletcher et al. 1989).

It is noteworthy that the rise in mean PAP did not exceed a value of 25 mm Hg during OLA, even though cardiac output increased by 30%. However, in studies conducted in patients with “damaged lungs”, greater increases in PA pressure accompanied by a decrease in RVEF have been reported to occur on PA ligation (Lewis-JW, Bastanfar et al. 1994; Cryer, Mavroudis et al. 1990; Pouleur, Lefevre et al. 1978). A question arises as to why differences exist between PA clamping and OLA? The answers may well be that

1. It can be speculated that the observed plateau in the rise of PA pressure during OLA is as a result of progressive diversion of flow to the NDL as PA pressure increases. Support for such a suggestion comes from the observation of progressive inhibition of HPV and an increase in shunt fraction during OLA seen with increases in PA pressure during OLA (Benumof 1991; Malmkvist, Fletcher et al. 1989; Malmkvist, Fletcher et al. 1989; Benumof and Wahrenbrock 1975) This increase in shunt fraction as PA pressure rises reflects an increase in diversion of pulmonary blood flow to the NDL. The impact of diversion of this

blood to the NDL is that it possibly acts as a safety mechanism limiting increases in PA pressure and other indices of opposition to pulmonary flow during OLA. This "blow-off effect" will protect the RV until PA clamping occurs.

2. The increases in mean PAP on PA clamping probably reflect the limited vascular reserve of the DL because of pre-existing pulmonary damage and loss of volume during OLA (Inomata, Nishikawa et al. 1997; Cohen and Eisenkraft 1996; Cohen 1995) This may be reflected by the large increases in PA pressure and PVR that are sometimes seen during PA clamping and pneumonectomy (Cryer, Mavroudis et al. 1990; Crouch, Lucas et al. 1987) as this "blow off effect" cannot occur.

Pulmonary arterial elastance rose by between 18 to 36% during OLA. This is further indicative that the opposition to pulmonary flow increased. It is also interesting that it appears that this increase in resistance was progressive as OLA continued (Table 3.3.1.12). However, no progressive increases in mean PAP were observed during the course of OLA.

Therefore, it can be concluded that the RV afterload did increase during OLA. The rise in PA pressures observed during OLA in the current study has been so commonly described before, that it is quoted in textbooks discussing the 'pathophysiology of OLA' (Chang, Black et al. 1996). This increase in afterload was accompanied by an increase in pulmonary artery impedance, (predominantly an increase in PA elastance). However, the purely resistive measurement of opposition to pulmonary flow, PVR, did not change. The current study represents the opportunity to investigate the significance of these increases in PA pressures and PA elastance on RV performance during OLA.

4.3 Control group: OLA and RV function

Stroke volume did not change from when the patients were awake to when OLA was instituted. This lack of change in stroke volume was observed in spite of the increase in cardiac index seen on initiation of OLA. No further differences in SV were observed during the course of OLA. Each factor determining stroke volume will be examined using the concept of coupling between a ventricle and its load i.e.

$SV = (Ved\text{-}Vo) - Pes/Ees$ ..... Equation 4.3.1 (Sagawa, Maughan et al. 1988) or

$SV = (Ved - Vo)/(1 + Ea/Ees)$ ..... Equation 4.3.2 (Fourie, Coetzee et al. 1992b).

The term Ved-Vo represents ventricular preload. Fluid management policy was to administer hydroxyethyl starch prior to induction of anesthesia to raise CVP by 3 mmHg. Intraoperative management was aimed at maintaining CVP at pre-induction levels. This policy resulted in no difference in either RV end-diastolic volume or filling pressure being recorded during any epoch in the control group (Table 3.3.1.11). This was in spite of potential decreases in venous return due to anesthesia induced vasodilatation (Thys, Dauchot et al. 1999), IPPV and hemorrhage that occurred in several patients. It must be stressed that RV preload has been shown to be *the* major determinant of right ventricular SV provided mean PAP does not exceed 35 mm Hg (Reuse, Vincent et al. 1990; Martyn, Snider et al. 1981). The mean PAP did not increase to greater than 25 mm Hg in the current study. This leads to the conclusion that the right ventricle operates during OLA in the current study, as a volume displacement or preload dependent pump (Hennebry and Gerstenblith 2001; Boldt, Kling et al. 1990). The corollary of the aforementioned statement is also important: that had preload not been constant, it would not have been possible to attribute changes

seen in RV performance purely to changes in RV afterload. Another observation is that preload forms part of the definition of wall stress, which in turn is one of the definitions of afterload intrinsic to the ventricle (Figure 1.4.1A and Equation 1.4.1.4). Had preload increased, it would have represented another form of increase of afterload for the RV.

The absence of a significant relationship between RVEDVI and either CVP or PAWP has been described in other studies (Table 3.5.3) (Reuse, Vincent et al. 1990). This is interesting as it was predetermined that fluid administration be titrated against cardiac filling pressures. It appears that using this method succeeded in maintaining a constant preload throughout the study period, despite the poor correlation between end-diastolic pressure and end-diastolic volume. It is possible that the clinician, who was not blinded to the happenings in theatre, titrated fluid against other parameters such as the MAP, heart rate, arterial pressure fluctuations associated with ventilation and ongoing blood losses. It is also possible that grouping all the RVEDVI and CVP data into one scatter plot is not a useful exercise as this hides the responses of individual patients (Thys and Dauchot 1998).

Neither RVEDVI nor SV changed on initiation of OLA or as OLA progressed. Thus, if equations 4.3.1 and 4.3.2 are studied, it is likely that Ees did not change from baseline. This conclusion could only apply if Vo and Pes did not change. Pes, as represented by mean PAP did however increase by 30% during OLA. In addition, Vo cannot be measured using the techniques currently available in theatre. Furthermore, although end-diastolic volume could be measured directly in this study, neither load independent variables of RV contractility such as Ees or preload recruitable stroke work (Karunanithi, Michniewicz et al. 1992) nor load dependent variables such as preload adjusted maximal power or dP/dt adjusted for RVEDV (Leather, Segers et al. 2000) could be measured in these studies. Instead, RVSWI, RVEF, and the relationship between right ventricular stroke work and indices of opposition to RV output were utilised as indices of contractility (Fourie, Coetzee et al. 1992b). The results of the current study indicate that, at these levels of increase (30%) in PAP, neither RVEF nor RVSWI differed from baseline. Ejection fraction is a load dependent parameter (Robotham, Takata et al. 1991). At constant RVEDV and with a 30% rise in mean PAP, as was seen in this study, an unchanged EF would represent an unchanged contractility compared to the baseline awake state (Robotham, Takata et al. 1991).

In essence, stroke work is the product of the (stroke) volume and pressure generated by the ventricle. Therefore when the LV is faced with increases in opposition to its ejection but stroke volume is maintained, the result is that stroke work will increase but at the cost of efficiency (Sagawa, Maughan et al. 1988). This relationship has been shown to hold for the RV as well (Fourie, Coetzee et al. 1992b). In a pig model utilizing glass bead embolism to induce pulmonary hypertension (Fourie, Coetzee et al. 1992b), it has been demonstrated that maximal RV efficiency occurred at a pulmonary elastance of 1 mm $Hg.ml^{-1}$. A pulmonary elastance of 1 mm $Hg.ml^{-1}$ corresponds to a mean PAP of 15 to 20 mm Hg. In the same model, maximal stroke work occurred at a pulmonary elastance of 1.8 to 2 mm $Hg.ml^{-1}$. A pulmonary elastance of 1.8 to 2 mm $Hg.ml^{-1}$ corresponds to a mean PAP of 30 to 40 mm Hg. When pulmonary elastance increased beyond this point, stroke work declined, the RV failed and began operating as a pressure pump (Fourie, Coetzee et al. 1992b; Sagawa, Maughan et al. 1988). Thus, RV performance usually only begins to deteriorate when indices of opposition to RV ejection reach 200 to 250% of baseline (Figure 4.3.1) (Fourie, Coetzee et al. 1992b). However, the exact relationship between SW and load will vary depending on the contractile

reserve of the ventricle (Figures 1.5.2.8 and 1.5.2.9).

If data from animal studies is applicable to humans, it is apparent that parameters of opposition to pulmonary flow indicating a transition from a flow to a pressure pump (i.e. pulmonary vascular elastance and mean PAP doubling and exceeding 1.8 mm Hg.ml^{-1} or 30 to 40 mm Hg respectively) were never reached in patients included in the control group of this study. Furthermore, the observation that RV stroke work index did not change with the increases in mean PAP during OLA implies that the right ventricle, at the levels of contractility exhibited by these patients, was not deleteriously affected by the 30% rise in mean PAP during OLA and continued to operate as a flow pump. It can therefore be concluded that during OLA, the right ventricle was still acting as a flow pump and never even approached the transition where it would function as a pressure pump (Fourie, Coetzee et al. 1992b). This implies that during OLA, the RV operates on the upward limb of the SW load relationship and there is RV reserve in terms of ability to generate more SW, should load increase.

There is a problem with the above view of RV function during OLA. There was a statistically significant increase in PAP during OLA. However, this rise in PAP was not accompanied by an increase in RV stroke work index. The question that needs to be addressed is whether the lack of change in RVSWI is explained by the RV operating on the flat part of the RVSWI-PA Ea relationship (see Figure 1.5.2.8). In other words, the RV was generating maximal stroke work during OLA. It has been suggested before that myocardial depression attributable to anesthesia per se resulted in both right and left ventricles operating on the peak of the SW-Ea relationship (Fourie 1989; Piene 1986; Piene and Sund 1982; Piene and Sund 1979). Can we be sure that RV function did not deteriorate during OLA? This question was addressed in two ways:

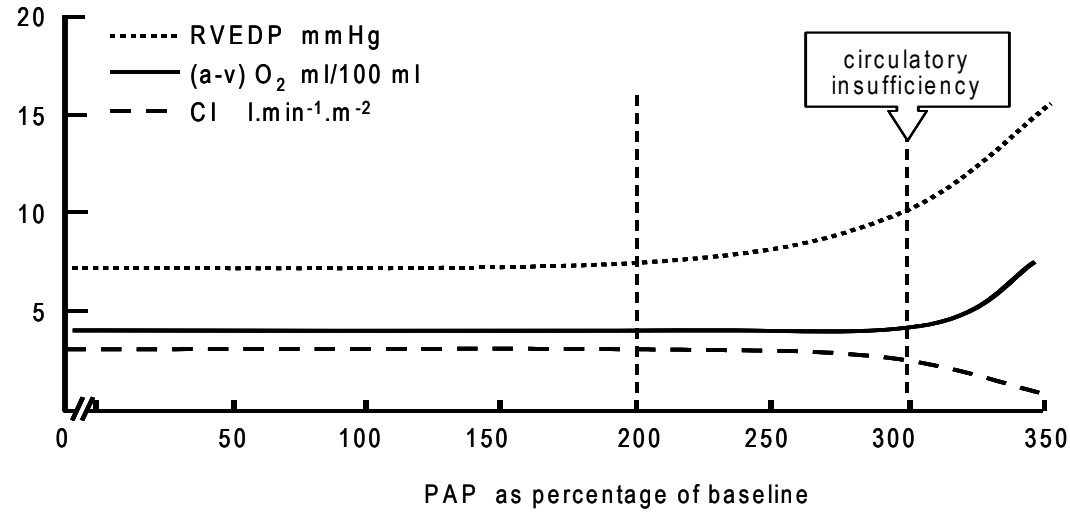


Figure 4.3.1 The effects of an increase in PAP on right ventricular performance and the consequences on systemic oxygen delivery. Note the large reserve and that deterioration of RV performance does not occur until PAP has increased by 250% of baseline. [PAP (%) is as a % of baseline mean PAP, where baseline mean PAP = 13.76 ± 3.02 mm Hg]. Fourie and Coetzee, 1992

1. A significant relationship (Figure 3.5.5) ($r = 0.5$, $p < 0.0001$, $n = 82$) exists between mean PAP and RVSWI during OLA in the control group. This indicates that while RVSWI did not increase during OLA for the whole group, increases in mean PAP did result in increases in RVSWI in individual patients. Why then did these rises in mean PAP during OLA not result in increases in RVSWI? The answer may lie therein that only a small percentage (25%) of RVSWI is accounted for by the increase in PAP. Furthermore, mean PAP only rose by 30%. It is entirely possible that the power of the current study was not sufficient to detect small changes in RVSWI. Using Sigmastat for Windows and the data in the current study, it can be calculated that between 21 and 25 patients are need to be studied to detect a significant increase in RVSWI. This is more than the number of patients enrolled in the control group of the current study.
2. To further address this question, individual patient changes in the RVSWI – Ea relationship were investigated. Firstly, the differences in RVSWI between the OLA and the awake steps were calculated for each patient. Secondly the differences between pulmonary elastance during the OLA and the awake steps were calculated for each patient. Thereafter, the RVSWI differences obtained for each individual patient were divided by the elastance differences for that patient. In this manner the slope of (i.e. the change in) the RVSWI-PA Ea relationship could be calculated for each patient. The mean slope of this relationship was +10.8 (95% confidence interval +2.3 to +19.3; 66 data points). The gradient is positive and the confidence interval does not include zero. This indicates that a positive gradient exists for the RVSWI-PA elastance relationship between the awake state and OLA. The conclusion can be made that in the majority of patients in the current study, the RV was operating on the upslope of the RVSWI versus Ea relationship. It supports the observation that RV function is well preserved during OLA.

In conclusion, regarding the indices of opposition to pulmonary flow and RV performance during OLA, it can be concluded that:

1. Opposition to RV ejection increases. This is evidenced by a 30% rise in mean PAP and 18 to 36% increase in pulmonary arterial elastance.
2. RVSWI, RVEF and stroke volume do not change during OLA compared with when the patients are awake or subjected to two-lung anesthesia. The conclusion is that coupling between the RV and its load is well preserved during OLA. It is likely that RV stroke work reserve is present during OLA. This would imply that the RV operates at close to maximal efficiency during OLA. (Figure 4.3.1).
3. PA elastance seems to deteriorate (i.e. increase) with time as OLA progresses. However, no evidence of time related changes in RV performance accompanied this progressive increase in elastance.

Thus, the hypothesis that the opposition to pulmonary flow increases during OLA has to be accepted. However, the sequitur that RV performance deteriorates when the indices of opposition to pulmonary flow increase during OLA is rejected. The alternative hypothesis, that RV performance is well maintained in the face of a moderate increase in PA pressure and PA elastance during OLA, is hence accepted.

Acceptance of the above conclusions must take into account the conditions prevailing in this study, which were as follows:

a. The patients included in this study represent a selected group of patients with pulmonary disease

and VO_2max greater than 11 ml.kg^{-1}.min^{-1} with no clinical evidence of pulmonary hypertension,

b. These subjects had no clinical abnormalities of LV function, systemic hypertension or myocardial ischemia. LV abnormalities would have interfered with the normal force transmission between the left and right ventricles,

c. They had acceptable RV coronary perfusion pressures,

d. RV preload was kept constant,

e. A moderately high dose of opioid and low dose of inhalation anesthetic agent was employed to provide anesthesia. This would have caused little myocardial depression,

f. A moderate sympathetic nervous system response to surgical stress accompanied OLA (see section 4.4.3),

g. The DLT's were correctly placed,

h. Limited tidal volumes were used to avoid excessive DL dynamic inflation and permissive hypercapnia was allowed. Approximately 5 cm intrinsic PEEP was present during OLA and,

i. A F_iO_2 of 1 to the DL and oxygen insufflation into the NDL.

Factor	Lung Influenced
Inspired oxygen concentration of anesthetic mixture 100% (Domino 1997)	DL
Preservation of lung volume by intrinsic PEEP during OLA (Myles 1996)	DL
P□O_2 increase during anesthesia (West 1985)	DL and NDL
Decrease in temperature with inhibition of HPV (Benumof and Wahrenbrock 1977)	DL and NDL
Blow off effect of the pulmonary vasculature of the NDL (see section 4.2 for explanation)	NDL
Selection of patients with sufficient pulmonary vascular reserve to undergo lung resection	DL and NDL
Inhibition of HPV by Isoflurane (Domino 1997; Benumof 1986)	DL and NDL
Adequate anesthesia levels with minimal catecholamine releases and little effect on PVR	DL and NDL

Table 4.3.1 Factors contributing to preserving a low PVR during OLA in this study.

This observation of preserved RV function with plenty of reserve is remarkable as one would expect that the effects of pulmonary disease, one lung anesthesia, positioning and IPPV would deleteriously affect the RV and its load.

Why does the frequently reported decrease in lung volume, lateral decubitus position and the onset of OLA, as demonstrated in the first group in Inomata and colleagues' study (Inomata, Nishikawa et al. 1997), not result in greater increases in any of the indices of opposition to pulmonary flow? Possible reasons for this phenomenon are outlined in Table 4.3.1. It may be concluded that conditions prevailing in this particular human model resulted in a low opposition to pulmonary flow compared with baseline levels. Therefore, the techniques used in this study are suitable for use in patients in whom further increases in opposition to RV ejection could compromise right ventricular performance.

4.3.1 Control group: factors affecting RV performance during OLA

The anesthetic agents in this study were maintained at constant levels for the duration of the period that the patients were observed. Isoflurane was administered at a relatively low end tidal partial pressure of 0.4 ± 0.2 to 0.5 ± 0.2 kPa, in combination with a moderately high targeted blood level 280 $ng.ml^{-1}$ using a target-controlled infusion of alfentanil. This particular combination of anesthetic agents (isoflurane and alfentanil) was chosen for the following reasons:

- The two agents act synergistically to produce "anesthesia" at concentrations used in this study (Glass, Shafer et al. 2000),
- The targeted plasma concentrations of alfentanil used in this study agree with those quoted by Glass, Shafer and Reves in a current textbook of anesthesia (Glass, Shafer et al. 2000) as being adequate to produce anesthesia in combination with a low level of inhalation agent (Table 4.3.2),
- It was unlikely that, in this selected group of patients, any individuals would have contraindications to this combination of drugs. Therefore, all patients could be exposed to the same combination of anesthetic drugs and hemodynamic effects should be similar in all patients,
- The effects of isoflurane on HPV during OLA have been well described and quantified. Furthermore, in the clinical setting of OLA, PaO_2 has been shown not to differ from agents (e.g. propofol) that do not inhibit HPV (Reid, Slinger et al. 1996) and,
- The moderately high dose opioid technique would hopefully avoid the confounding issue of sympathetic nervous system stimulation in response to the surgical assault and produce little myocardial depression (Coetzee 1993; Frostell, Blomqvist et al. 1993). This would enable comparability between the epochs.

The computer controlled infusion employed the model described by Maitre and colleagues to maintain the predetermined alfentanil plasma concentrations (Maitre, Ausems et al. 1988; Maitre, Vozeh et al. 1987). Actual plasma concentrations that are achieved using computer controlled infusions of alfentanil may vary by 20 to 30% of predicted and Maitre and colleagues' model has been reported to have a median performance error of approximately 53% (Figure 4.3.1.1) (Glass, Shafer et al. 2000; Westmoreland, Sebel et al. 1994; Coetzee 1993). These variations are considered to be within a clinically acceptable range (Glass, Shafer et al. 2000; Coetzee 1993).

Isoflurane has been reported to produce a dose dependent negative inotropic effect (Frostell, Blomqvist et al. 1993; Coetzee, Fourie et al. 1987b). It is however apparent that the anesthetic agents employed in this study, in combination with surgical stimulation and fluid loading, exhibited no clinically measurable deleterious effects on right ventricular performance. This observation must be contrasted with reports in which inhalation anesthetic agents compromised RV stroke work and efficiency (Piene 1987; Priebe 1987; Elzinga, Piene et al. 1980; Piene and Sund

1979).

Depth of anesthesia	Plasma concentration of alfentanil
The steady state plasma concentration that causes 50% reduction in MAC of isoflurane in 50% of patients	50 $ng.ml^{-1}$
The steady state plasma concentration that prevents somatic or autonomic response to skin incision in 50% of patients	200 – 300 $ng.ml^{-1}$
Recommended levels for minor surgery when combined with 67% nitrous oxide	100 – 300 $ng.ml^{-1}$
Recommended levels for skin incision when combined with 67% nitrous oxide	200 – 300 $ng.ml^{-1}$
Recommended levels for major surgery when combined with 67% nitrous oxide	250 – 400 $ng.ml^{-1}$

Table 4.3.2 Adapted from Glass, Shafer et al. 2000

As discussed in the literature review, early studies indicated that, in its normal state and facing a normal opposition to ejection, the RV generates maximal stroke work (Piene 1987; Elzinga, Piene et al. 1980; Piene and Sund 1979). This contention was subsequently refuted, when it was demonstrated that the normal RV, like the LV, works at maximal efficiency and possesses a significant stroke work reserve (Hennebry and Gerstenblith 2001; Coetzee and Fourie 1993; Fourie, Coetzee et al. 1992; Fourie 1989; Piene and Sund 1982). The reasons for the discrepancy between early and later studies were hypothesized to be that the anesthetic techniques used in these animal models (e.g. high concentrations of halothane or barbiturate infusions) (Asanoi, Sasayama et al. 1989; Sagawa, Maughan et al. 1988), combined with the effects of cardiac denervation (Fourie, Coetzee et al. 1992a; Burkhoff and Sagawa 1986; Piene and Sund 1982), deleteriously affected RV performance. The preservation of SW reserve of the RV under the balanced anesthesia technique and loading conditions employed in this study is therefore an important observation.

Boyd and colleagues compared the effects of propofol and isoflurane on RV function in patients with peripheral vascular disease undergoing lower limb bypass surgery (Boyd, Murdoch et al. 1994). They concluded that right ventricular performance as measured by cardiac output (4.0 vs. 4.5 $l.min^{-1}$), RVEF (35.1 vs. 39.4%), stroke volume (35.4 vs. 39.6 ml) and RVEDVI (102 vs. 110 $ml.m^{-2}$) was better preserved with propofol than isoflurane. They observed no difference in MAP or heart rate between the groups. From this observation they concluded firstly that sympathetic nervous system stimulation was not a factor that differentiated the cardiac effects of either technique, and secondly that their anesthetic techniques were of similar depth. They suggested that propofol might be more suitable than isoflurane in patients who may already have impaired right ventricular function and in whom maintaining a high cardiac output may be beneficial. This conclusion would be of relevance to patients undergoing OLA. However, their conclusion that one anesthetic technique (propofol infusion) is superior to another (isoflurane) in patients with depressed RVF is probably an overstatement of fact for the following reasons:

- Isoflurane and propofol resulted in only a 10% difference in cardiac index, SI and RVEF. Albeit these changes were statistically different, it is questionable as to whether they are of clinical significance, and whether their firm conclusion is justified based on the strength of the differences they observed. One concern is that the variation in cardiac output with thermodilution is approximately 10 %. This difference is within the observed 10% measurement error of the thermodilution method used in their study.
- These authors claim to have used equipotent anesthetic dosages (Boyd and Grounds 1996). This may not in fact be the case as the dosage of anesthetic agent was titrated to unsophisticated endpoints. The method they used to determine equivalent levels of anesthetic agent was that the end tidal isoflurane concentration was adjusted within a *range* of 0.5 to 1.0 MAC and computer controlled infusion of propofol concentration was adjusted "*until satisfactory anesthesia was achieved. … Anesthesia was judged to be satisfactory on the basis of an aggregate of clinical signs used daily to control and monitor the depth of anesthesia. The patients had to have a heart rate less than 15% above control and a systolic blood pressure less than 15% above control, as well as no evidence of sweating or tears.*"
- Although relative MAC and MIR for each agent was similar, the presence of cardiac disease and the use of cardiovascular medication by the vascular surgery patients involved in this study could also account for the different responses of the two anesthetic regimes.
- Isoflurane produces a dose dependent decrease in contractility of both ventricles (Pagel, Farber et al. 2000). However, the negative inotropic effects of propofol exhibit hysteresis with myocardial function failing to return to baseline as plasma levels decrease (i.e. myocardial depressant effect prolonged beyond the decay in propofol concentrations) (Coetzee 1993; Coetzee, Fourie et al. 1989). Albeit propofol is perceived by these authors to be less deleterious for RV function, the administration of constant infusions or additional boluses may result in plasma propofol concentrations reaching levels that compromise ventricular function. In contrast to these risks posed by propofol boluses, one safety mechanism of inhalation anesthetic agents is that their partial pressures in plasma cannot increase above that of the dialled in concentration (Coetzee 1993).
- Propofol appears to have profound effects on the pulmonary circulation, predominantly causing or potentiating pulmonary vasoconstriction:
  - It has been shown to cause pulmonary hypertension in pigs (Coetzee 1993),
  - Propofol increases the myofilament calcium sensitivity of dog PA smooth muscle. This led to increases in the tension developed by propofol treated PA muscle strips compared with control (Tanaka, Kanaya et al. 2002),
  - Propofol has been shown to increase the tension in response to phenylephrine produced by canine PA rings (Ogawa, Tanaka et al. 2001),
  - This anesthetic drug has also been demonstrated to potentiate the effects of sympathomimetics on the pulmonary circulation (Kondo, Kim et al. 2001),
  - Propofol has been shown to attenuate endothelium-dependent pulmonary vasodilatation (Kondo, Kim and Murray 2000) and,
  - Propofol has also been demonstrated to potentiate HPV (Nakayama and Murray 1999),

  Therefore propofol may well increase PA pressure and concomitantly decrease RV contractility. This is a potentially dangerous combination in patients with severe pulmonary disease.

In subsequent correspondence in the British Journal of Anaestheia, Boyd and colleagues stated that they "took considerable care to compare similar anesthetic dosages of propofol and isoflurane" (Boyd and Grounds 1996). They comment furthermore, "*observations of cardiac function should be made during periods of steady state anesthesia."* These principles are applicable to a study conducted by Boldt and colleagues (Boldt, Muller et al. 1996). In both the Boldt and the Boyd studies, an RVEF catheter was used to compare the effects of two anesthetic techniques in patients undergoing pneumonectomy and lobectomy. In the Boldt study, one anesthetic technique used was fentanyl, nitrous oxide, propofol and vecuronium. The other technique comprised fentanyl, midazolam and vecuronium. The results of the Boldt study indicated that the anesthetic regimen *itself* did not result in any differences in hemodynamics or RV function. Rather it was the procedure (pneumonectomy or lobectomy) that played the key role in determining hemodynamics. However, certain deficiencies in methodology are apparent in Boldt's study. Albeit "one size does not fit all", one wonders if the anesthetic techniques of titration against clinical effect fulfil the criterion of comparability in terms of depth of anesthesia as mentioned by Boyd. For example, significantly different dosages of fentanyl were used in two of the groups and there was a significantly lower heart rate in the propofol-nitrous oxide than in the midazolam-fentanyl group. These observations suggest the presence of different anesthetic depths in the groups. The difference in depth of anesthesia may have resulted in differing autonomic responses to surgery. These differences make it difficult to compare RV function and other hemodynamic parameters between the groups.

Kellow and colleagues (Kellow, Scott et al. 1995) compared the hemodynamic and right ventricular effects of isoflurane with propofol. The isoflurane was administered at an inspired concentration of 1 to 1.5% but neither fresh gas flow nor end tidal isoflurane concentrations were reported in the paper. The propofol infusion was administered initially at 10 $mg.kg^{-1}.hour^{-1}$ and was progressively reduced at 10 minute intervals to 8 and finally to 6 $mg.kg^{-1}.hour^{-1}$. 50% nitrous oxide in oxygen was co-administered during OLA. In contrast to the Boyd study, this study by Kellow and colleagues came to a different conclusion, namely that RV systolic function, as judged by RVEDVI, RVEF, and CI, was more deleteriously affected by propofol and nitrous oxide mixture than isoflurane. The reductions in systolic

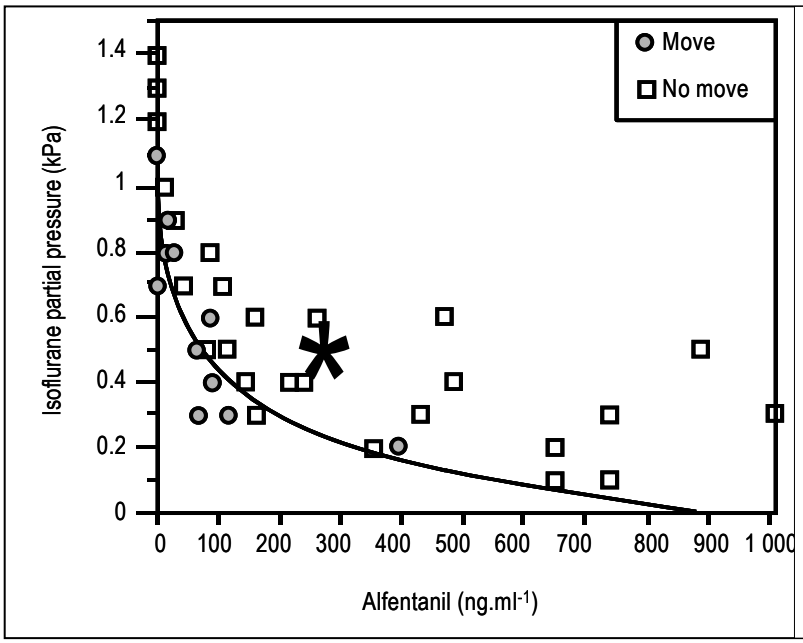


Figure 4.3.1.1 Relationship between of end tidal isoflurane concentration and mean alfentanil concentrations for each patient. Each point represents the move/no move response for an individual patient. The line represents the 50% likelihood of movement to skin incision. The patients in the current study are represented by the star.* Redrawn from Westmoreland, Sebel et al, 1994.

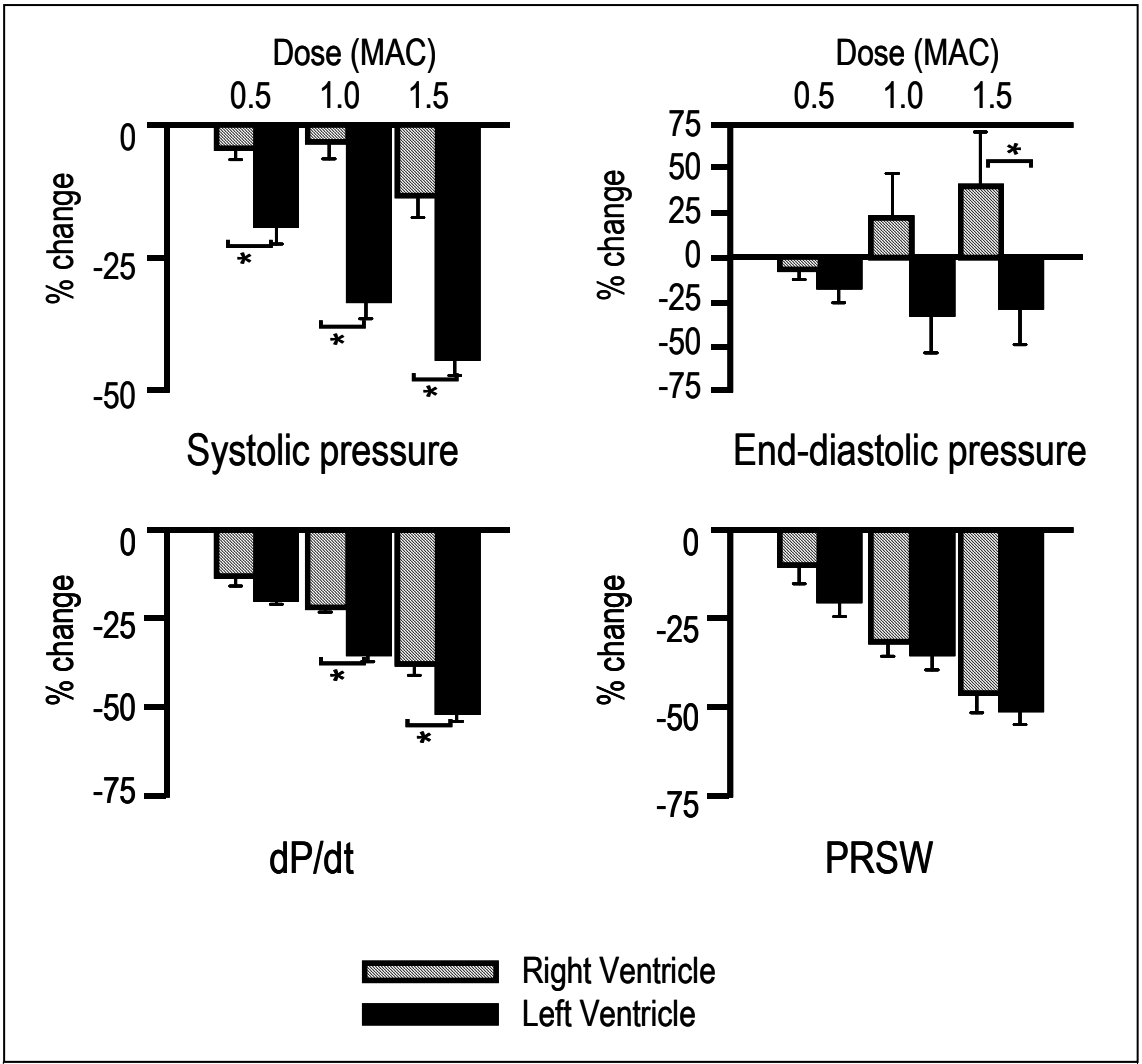


Figure 4.3.1.2 *Isoflurane induced changes in RV and LV function. The parameters are standardized as a percentage change from baseline. PRSW = preload recruitable stroke work. n = 6. * Indicates RV and LV differ, p < 0.05. Modified from Heerdt, Gandi and colleagues, 1998*

function also persisted in the propofol group after the infusion was stopped. Similar observations have also been demonstrated for the LV (Coetzee 1993; Coetzee, Fourie et al. 1989). Thus, Kellow's study confirms that RV function is also deleteriously affected by propofol and this effect lingers after terminating the infusion. As mentioned previously, this raises questions regarding the suitability of propofol anesthesia in patients whose RV systolic performance is at risk. Furthermore in the Kellow study, hemodynamics during OLA when anesthesia was conducted with isoflurane did not differ from baseline. This is contrary to the findings in the Boyd study but similar to observations made in the current study. Again, as in the Boldt and Boyd studies, the anesthetic depth in the two groups in the Kellow study may not be comparable, a factor which may confound their findings.

There are other points of interest in the Kellow study:

- In both the Kellow study's isoflurane group and in the current study, surgical stimulation during OLA restored the cardiac index to baseline. Similar increases in cardiac output on initiation of OLA have been reported in other studies (Pagel, Fu et al. 1998; Abe, Mashimo et al. 1998; Zaune, Knarr et al. 1990; Cohen, Eisenkraft et al. 1988; Thys, Cohen et al. 1988; Aalto-Setala and Heinonen 1982; Aalto-Setala,

Heinonen et al. 1975). In the light of these increases in cardiac output, could it be that the sympathetic nervous system activity counterbalanced the negative inotropic effects of the inhalation agent but not those attributable to propofol?

- Another point to note in the Kellow study is that shunt fraction was threefold greater in the isoflurane group than in the propofol group during OLA. Kellow and colleagues' study therefore highlights the divergent influences on hemodynamics and oxygenation, aggravated by propofol and isoflurane respectively, during thoracic anesthesia. These problems led these investigators to conclude that neither propofol nor isoflurane are ideal anesthetic agents during OLA. This conclusion opens the possibility that the balanced anesthetic techniques used in the current study may result in less depression of both RV function and HPV than when using a single agent in higher dose during OLA. Albeit isoflurane and other inhalation agents have been shown to produce progressive myocardial depression, low dosages of isoflurane in the order of magnitude used in the current study have been demonstrated to produce little myocardial depression (Coetzee, Fourie et al. 1987b). Dosages of alfentanil have been demonstrated to produce decreases of sympathetic nervous system tone but little or no myocardial depression (Bailey, Egan et al. 2000; Heerdt, Gandhi et al. 1998; Coetzee 1993). However, a report of the effects of the *combination* of alfentanil and isoflurane on hemodynamics and oxygenation could not be found using a Medline search of the literature.

- Decreases in systemic arterial pressure of up to 30%, and LVSWI of between 21 to 43% occurred after induction of anesthesia in our patients. However, indices of RV afterload increased moderately while RVSWI did not change after induction of anesthesia or during OLA. Therefore the anesthetic technique in the current study resulted in a decrease in the parameters of **left** ventricular afterload and stroke work. This is in contrast to the moderate increase in RV afterload and absence of change in the indices of RV performance during both two and one lung anesthesia. The differing effects of similar dosages of anesthetic agents on coupling of the two ventricles and their respective loads were elegantly studied by Heerdt and co-workers (Heerdt, Gandhi et al. 1998). They described disparate effects of increasing dosages of isoflurane on afterload and work performed by the right and left ventricles of pentobarbital anesthetised swine. Heerdt et al. observed that progressively increasing partial pressures of isoflurane produced similar effects on contractility of both ventricles. However, left and right ventricular afterload was affected very differently by increasing dosages of isoflurane. LV afterload and work decreased in a dose dependent manner while indices of RV afterload and RV work per unit time (power output) actually increased as the partial pressure of isoflurane progressively increased. The result of this was to impair the coupling between the RV and its load. Usually, the vasodilatation induced by clinically useful concentrations of isoflurane more than compensates for its negative inotropic effects on LV. The usual result is that the LV stroke work and the effectiveness circulation as a whole, is well preserved. Heerdt however suggests that reports in which isoflurane have been shown to decrease cardiac output by as much as equipotent dosages of halothane may be due to the deleterious effects of inhalation anesthetic agents on RV-PA coupling.

Therefore, as demonstrated again in the Heerdt study, the anesthetic technique used has significant effects on RV function and coupling to its load. This consideration may be of special relevance in circumstances where RV function

is compromised. It emphasizes that the anesthetic technique used in the current study avoids deleteriously influencing RV performance. However, care should be taken when the results of the current study are extrapolated outside the particular "human model" that was used.

Heerdt's study raises the issue of the influence of left ventricular function on that of its counterpart. Mean arterial blood pressure decreased by 20% after induction of anesthesia in the current study. This decrease in aortic pressure was accompanied by a greater than 30% rise in PAP. This had the effect of decreasing RV coronary perfusion pressure (CPP) by 30% from 80.3 when awake, to 56.5 mm Hg while anesthetised ($p < 0.001$). Vlahakes and colleagues (Vlahakes, Turley et al. 1981) demonstrated that after greater rises in right-sided pressures than were observed in the present study (RV systolic pressure 54 ± 13 mm Hg and RV coronary perfusion pressure 41 mm Hg), coronary vascular reserve was well preserved. Only at the point of circulatory collapse (RV systolic pressure of 61 ± 10 mm Hg and coronary perfusion pressure 23 ± 9 mm Hg), did RV ischemia become an issue in their dog model (Vlahakes, Turley et al. 1981). However, during OLA, the RV in the control group of the current study was not stressed by severe increases in afterload or an increase in RVEDVI, as was the case in the Vlahakes study. Therefore, it is unlikely that this small decrease in coronary perfusion pressure represented a clinically significant decrease in RV perfusion pressure in these patients.

A dual inflexion was observed in 83.5% of the electronically recorded RV and PA pressure tracing (Figure 4.3.1.3). This raises the contention that LV systolic interaction between the ventricles may play a significant role in right heart performance. This double hump in the RV and PA pressure versus time recordings has been observed and investigated by Santamore's group (Santamore and Gray, Jr. 1996; Damiano, Jr., La Follette, Jr. et al. 1991). Damiano and colleagues (Damiano, Jr., La Follette, Jr. et al. 1991) demonstrated that the first component of the pressure wave is directly related to RV contraction, whereas the second part is related to left ventricular contraction. It is remarkable that the LV component comprised the dominant fraction of both the PA and RV contraction (Table 4.3.3) (Santamore and Gray, Jr. 1996; Santamore, Constantinescu et al. 1988a; Santamore, Lynch et al. 1976b). Although the percentage contribution of each component of the double hump was not measured in this study as was done by Damiano and colleagues, we have no reason to suspect that this form of systolic interaction is *not* the reason behind the double inflexion in the PA and RV pressure-time tracings in this study. The implication is that the LV contributes a significant portion of the energy to the forces propelling blood through the pulmonary vasculature (Woodard, Chow et al. 1992; Slinker and Glantz 1986; Elzinga, Piene et al. 1980; Pool, Piggott et al. 1976). Because of the aforementioned consideration, exclusion criteria for our patients included the presence of clinical abnormalities of LV function. The implications for the current study are that RV performance is well preserved during OLA when LV function is intact. The corollary is that impairment of LV function may significantly impair RV function during OLA because of both decreased systolic interaction between the ventricles and a raised LVEDP that frequently accompanies LV systolic and diastolic dysfunction (Marshall and Marshall 1997).

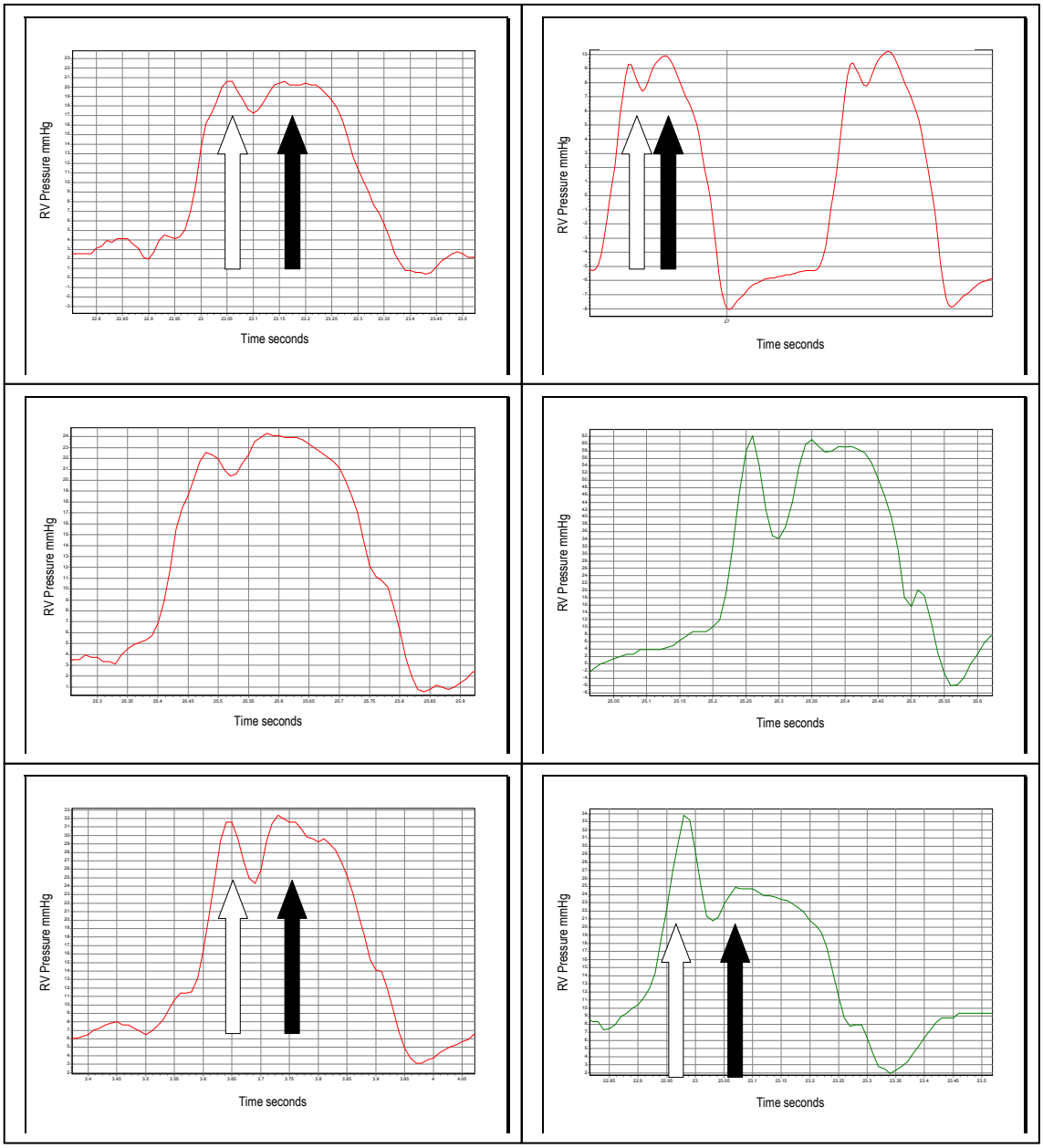


Figure 4.3.1.3a *Six RV pressure versus time recordings. These recordings were imported from Alab. They demonstrate the "double hump" in the pressure trace. Electronic recordings were made in 24 subjects and comprised 396 tracings, 200 of the PA and 196 of the RV. In 32 RV and 33 PA tracings, which comprise 16.5% of the total of the tracings, double peaks did not appear or were obscured by ringing. Solid white arrows represent the RV and solid black arrows represent the LV part of the recordings.*

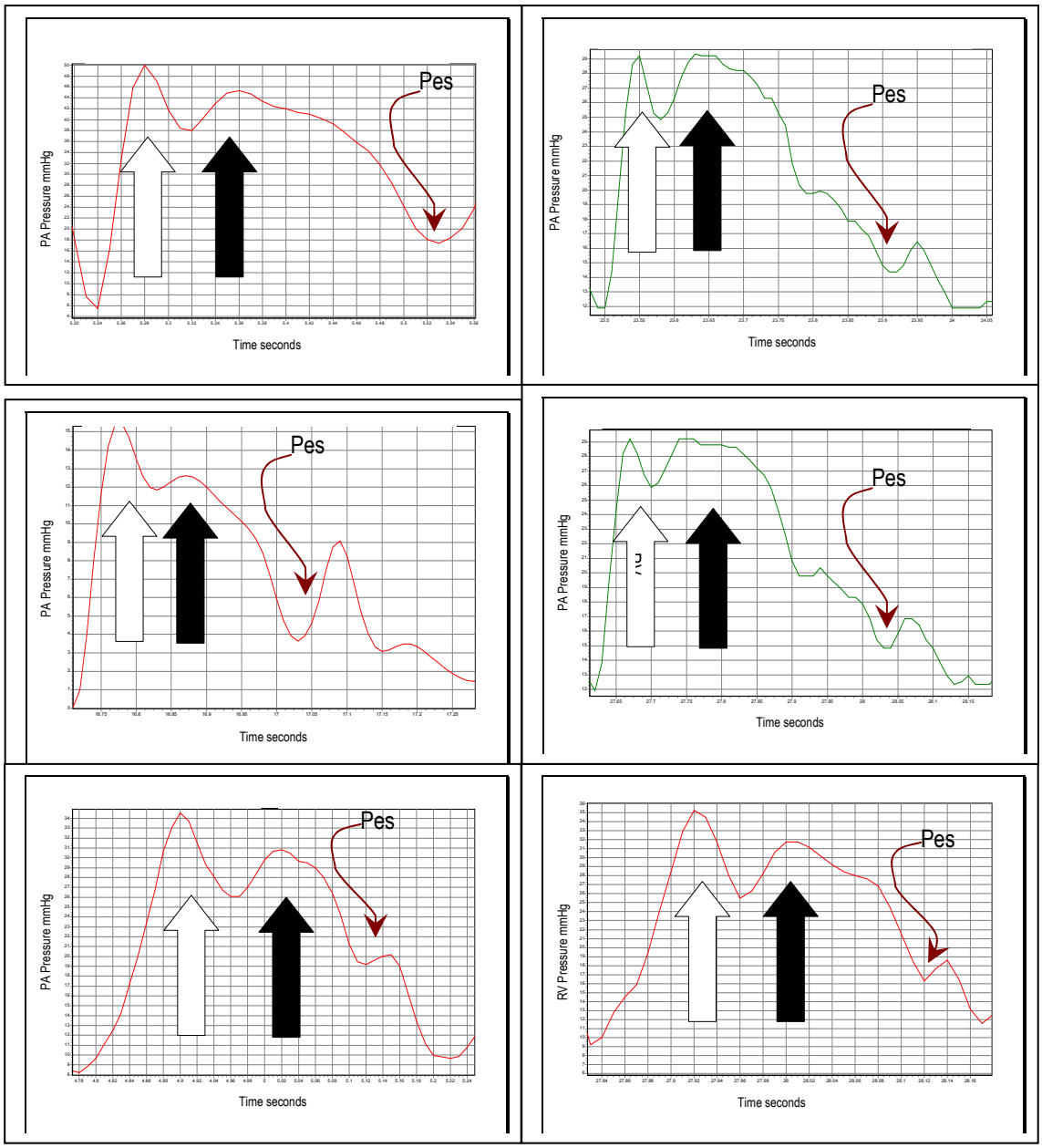


Figure 4.3.1.3b *Six PA pressure versus time recordings. These recordings were imported from Alab. They demonstrate the "double hump" in the pressure trace. Electronic recordings were made in 24 subjects and comprised 396 tracings, 200 of the PA and 196 of the RV. In 32 RV and 33 PA tracings, which comprise 16.5% of the total of the tracings, double peaks did not appear or were obscured by ringing. Solid white arrows represent the RV and solid black arrows represent the LV part of the recordings.*

Another explanation as to why this double hump may occur relates to the dual embryonic origins of the RV outflow tract (Raines, LeWinter et al. 1976; Armour, Pace et al. 1970). The RV inflow tract contracts 25 to 50 milliseconds before the outflow tract. The effect is that RV contraction occurs in a peristaltic manner (Heerdt and Pleimann 1996; Meier, Bove et al. 1980; Raines, LeWinter et al. 1976). This results in intraventricular pressure gradients occurring within the RV (Heerdt and Pleimann 1996; Raines, LeWinter et al. 1976; Armour, Pace et al. 1970). Furthermore, the RV outflow tract exhibits a greater response to inotropic agents with elevation of the normal intraventricular pressure gradient (Heerdt and Pleimann 1996; Armour, Pace et al. 1970). However, as the partial pressure of halothane (Heerdt and Pleimann 1996) or isoflurane (Priebe 1987) is increased, this gradient is firstly minimized and eventually abolished at 2 MAC halothane. Heerdt and Pleimann (Heerdt and Pleimann 1996) showed that the normal disconcordance of RV contraction is abolished because inhalation anesthetic agents delay the inflow tract contraction to be synchronous with that of the outflow tract. This results in the abolition of the RV intraventricular pressure gradient on administration of even low dosages of inhalation anesthetic agents (Meier, Bove et al. 1980). Furthermore, the differences in time between contraction of the inflow and outflow regions of the RV are significantly shorter than that seen between the double peak (90 to 120 milliseconds) of the RV and PA tracings (Hennebry and Gerstenblith 2001). Thus, for the reasons outlined above, it is unlikely that these double pressure peaks are due to disconcordance of RV inflow and outflow tract contraction.

	LV component %	RV component %
PA: Peak to Peak	67.5	32.5
PA: Root-mean-square value	68.3	31.8
RV: Peak to Peak	63.5	36.5
RV: Root-mean-square value	65.2	34.8

Table 4.3.3 The relative left and right ventricular contributions to pressures driving blood across the pulmonary vasculature. Data reproduced from Santamore (Santamore and Gray, Jr. 1996).

Murgo and Westerhof (Murgo and Westerhof 1987) describe a midsystolic inflexion followed by a late systolic pressure rise in both the LV, aortic, and RV and PA pressure tracings when significant wave reflection is present. Beats demonstrating such a phenomenon are termed type A beats. The input impedance spectrums of type A beats demonstrate large oscillations around the characteristic impedance. These oscillations indicate that significant wave reflection is present. Murgo and Westerhof termed beats without the double pressure peak, that are associated with low peripheral vascular resistance and a nonoscillatory input impedance spectrum, type C beats. During normal circumstances, the pulmonary circulation produces little wave reflection and the beats do not demonstrate a double peak, and are typical of type C beats. Using a catheter with multiple sensors, they concluded that the systemic vascular reflection originates primarily around the renal arteries, but there has been no such study of the origins of wave reflection in the pulmonary circulation during PHPT (Murgo and Westerhof 1987). No conclusions for or against this particular cause of the dual inflexion can be made in the present study.

One last possibility is that the low resonant frequencies of the PA catheter-transducer system produced artefacts in the PA waveform. It is unlikely that amplification due to ringing was the sole reason for these double peaks. The reason why this explanation is unlikely to provide the sole reason is that these double peaks occur with great consistency. Furthermore, too many other plausible explanations exist for them to be considered purely artefactual.

Cardiac index and oxygen delivery both decreased during two-lung anesthesia compared to the measurements made when the patients were awake (Tables 3.3.1.10 and 3.3.1.16). Similar observations were made in Kellow's study (Kellow, Scott et al. 1995). Attenuation of sympathetic nervous system tone can occur after administration of any of the synthetic opioids currently in use (Bailey, Egan et al. 2000; Thys, Dauchot et al. 1999; Coetzee 1993). This will explain the decreases in cardiac output and oxygen delivery seen in the current study.

However, moderately high dose opioid administration combined with inhalation anesthetic agents, at partial pressures that exceed MAC awake, do not necessarily achieve the levels needed to block autonomic responses to surgical stimulation (MAC BAR) (Bailey, Egan et al. 2000; Stanski 2000). In the presence of 70% nitrous oxide, the plasma concentration of alfentanil needed to produce a 50% chance of suppressing increases of heart rate and blood pressure in response to skin incision (Cp_{50}) is 279 ± 20 $ng.ml^{-1}$ (Stanski 2000). For intraoperative manipulation, Cp_{50} varied between 270 ± 63 to 412 ± 135 $ng.ml^{-1}$ for breast and upper abdominal surgery respectively (Stanski 2000). The targeted concentrations of alfentanil used in the current study were 280 $ng.ml^{-1}$, in combination with a partial pressure of 0.5 ± 0.2 kPa isoflurane. This represents a depth of anesthesia less than in Stanksi's study (Stanski 2000). It is therefore possible that approximately 50% of patients in the current study could have exhibited endogenous catecholamine release in response to surgical manipulation. Surgical stimulation was permitted only after the "2 lung anesthesia" measurements had been completed. The decreases in cardiac index and oxygen delivery observed immediately after induction of anesthesia were restored to baseline once surgery commenced, as observed in other studies (Abe, Mashimo et al. 1998; Boldt, Papsdorf et al. 1997; Cohen, Eisenkraft et al. 1988). Furthermore, an increase in heart rate was observed once surgical manipulation commenced. This constitutes evidence that the levels of anesthesia employed in this study were able to blunt but was inadequate to abolish the autonomic response to surgical incision. However, the partial pressure of isoflurane exceeded MAC awake and was sufficient to prevent explicit recall and movement in response to surgical stimulation (only the initial dose of muscle relaxant was given and not repeated) (Stanski 2000).

Endogenous catecholamine release in response to surgical stimulation may however provide an advantage by increasing RV contractility. This may result in an improvement in coupling between the ventricle and its load, if concomitant increases in RV afterload do not occur. Thus, the possible positive inotropic stimulation that occurred concurrently with OLA in this study, may have further counteracted the already minimal cardiac depressant effects of the anesthetic agents and contributed to the preservation of RV function. The cardiovascular effects of anesthesia are frequently the result of a balance between on the one hand, myocardial depression, vasodilatation, and sympathetic nervous system depression induced by the anesthetic agents and, on the other hand, the sympathetic response to surgical stimulation (Pagel and Warltier 1997).

Although increases in sympathetic nervous system stimulation undoubtedly play a role in the increased oxygen delivery, cardiac index and heart rate on initiation of OLA, is this mechanism solely responsible for such powerful and immediate restoration of hemodynamics to baseline (Abe, Mashimo et al. 1998; Boldt, Papsdorf et al. 1997; Cohen, Eisenkraft et al. 1988)? Could it be that release of neurohumoral factors induced by the onset of OLA are also responsible for this phenomenon? The lung is an active metabolic organ that renders inactive the circulating vasoconstrictory substances that bombard its vast vascular endothelium (Taylor and Lausch 2001; Boldt, Papsdorf et al. 1997; Rodman and Voelkel 1997; Scherer, Van Aken et al. 1984). Pre-existing lung disease and collapse during one lung anesthesia may affect the way circulatory mediators are metabolised (Taylor and Lausch 2001; Boldt, Papsdorf et al. 1997). In addition, the increase in pulmonary blood flow such as occurs in the DL during OLA, will induce vasodilatation mediated by nitric oxide, prostaglandins, and acetylcholine. These mediators may spill over into the circulation and influence systemic hemodynamics (Scherer, Van Aken et al. 1984). It has also been suggested that the collapsed ischemic NDL may produce vasoconstrictory substances such as endothelin (Rodman and Voelkel 1997). Boldt and colleagues (Boldt, Papsdorf et al. 1997) therefore studied the concentrations of a number of vasoconstrictors, noradrenaline, vasopressin and endothelin, during OLA. Of these, only noradrenaline levels were raised during OLA. It is however notable that higher levels of noradrenaline were observed in the pneumonectomy group. In the same study, Boldt and colleagues also described increases in vasodilatory substances during OLA. Atrial natriuretic peptide and 6-keto-prostaglandin $F_{1\alpha}$ showed tendencies to rise during OLA. Scherer and co-workers (Scherer, Van Aken et al. 1984) also demonstrated raised vasodilatory prostaglandin E_2 and decreased vasoconstrictor F_2 during both one *and* two-lung ventilation. Scherer commented that increased levels of vasodilatory substances could result in inhibition of HPV during OLA, although he himself could not demonstrate a relationship between shunt fraction and an increase in PGE_2 levels (Scherer, Van Aken et al. 1984). In the current study, hormonal levels were not measured, but the indices of systemic vascular resistance did not decrease during OLA compared to 2-lung anesthesia. Even though the changes in the abovementioned vasoactive mediators do occur during OLA, I suspect that the hemodynamic changes seen in the current study are mainly attributable to stress related to the surgical stimulation, as the rapid changes seen are so typical of sympathetic nervous system stimulation.

It is also possible that the catecholamines released in response to surgical stimulation contributed to increases in PA pressure and decreases in PA compliance (Liu and Barnes 1997). Marshall and Marshall point out that such catecholamine-induced changes are not sustained. This is because the lungs' possess many mechanisms to prevent vasoconstriction: these mechanisms eventually predominate over the vasoconstrictory stimuli (Marshall and Marshall 1997). This override of vasoconstrictory influences does not occur if vasoconstriction is due to hypoxia, an issue that was certainly not the case in this study (Marshall and Marshall 1997). Furthermore, West suggests that if PVR is already low further insults such as sympathetic nervous system stimulation will have less effect on pulmonary vascular tone (West 1985). Thus, the endogenous release of catecholamines most likely had minimal effect on the already low PA tone in this study.

In the face of an increased afterload, both right and left ventricles have been reported to be capable of generating either homeometric and/or heterometric autoregulatory responses (Calvin, Jr. 1991). As long ago as 1912, Von Anrep first suggested that a ventricle facing an increase in afterload would exhibit an increase in contractility (Calvin,

Jr. 1991; Coetzee, Fourie et al. 1987a). This phenomenon was described as homeometric autoregulation because the increase in contractility occurred without an increase in ventricular end-diastolic volume (Calvin, Jr. 1991). Homeometric autoregulation may however be the result of a very steep Ees relationship and very small increases in EDV of the ventricle, which easily compensate for an increase in afterload (Coetzee, Fourie et al. 1987a). This phenomenon therefore depends to a large degree on the state of contractility of the ventricle (Coetzee, Fourie et al. 1987a). The Anrep effect has also been associated with increases in heart rate, the so-called Bodwitch effect. The mechanism underlying the Bodwitch effect has been attributed to increased sarcolemmal calcium concentrations. A further mechanism, that of increased coronary blood flow induced by systemic hypertension, has also been suggested to underlie this phenomenon (Calvin, Jr. 1991).

Does this phenomenon occur in ventricles with lesser contractile reserve such as the RV or those depressed by anesthetic agents? Homeometric autoregulation has been shown to exist in the right ventricle of newborn lambs. This was demonstrated by an increase in Ees during infant respiratory distress syndrome (Lopes, Steendijk et al. 2000). However, the neonatal RV is a much thicker walled chamber than that of its adult equivalent and may possess greater contractile reserve, hence explaining the aforementioned observation. Calvin has however also reported the existence of homeometric autoregulation in the RV facing pulmonary glass bead embolism (Calvin, Jr. 1991). He could however not distinguish this phenomenon from metabolic effects secondary to the vascular damage caused by embolism (Calvin, Jr. 1991). In the current study, load independent indices of contractility such as Ees or PRSW were not measured; however, indirect indices of RV contractility (such as RV ejection fraction and RVSWI) and stroke work did not change as PA pressure and elastance increased on initiation of OLA. Thus, there is no evidence of homeometric autoregulation in this study. The reasons may be that:

- Increased coronary blood flow is a prerequisite for the Anrep effect. In the current study, this did not increase because RV perfusion pressure did not increase during OLA (Calvin, Jr. 1991),
- The moderate increases in PA pressures seen in this study are of insufficient consequence to the RV to induce such a phenomenon,
- The indices representing contractility in the current study were not sensitive enough to detect this phenomenon,
- Homeometric autoregulation is impaired or even abolished by anesthesia (Coetzee, Fourie et al. 1987a) or,
- Neither ventricle actually exhibits homeometric autoregulation, and alternative explanations account for the phenomenon (Coetzee, Fourie et al. 1987a).

Coetzee and colleagues (Coetzee, Fourie et al. 1987a) found no evidence of Anrep's effect and questioned the existence of homeometric autoregulation under anesthesia. They did however demonstrate that in response to a 40% increase in MAP, under similar levels of anesthesia (0.7% inspired isoflurane) to those used in the current study, that *heterometric* autoregulation (also termed preload reserve or Frank Starling mechanism) preserved left ventricular stroke work of anesthetised dogs. Calvin has also demonstrated that heterometric autoregulation is a relevant concept in the ***right*** ventricle of dogs subjected to an increase in afterload by pulmonary glass bead embolism (Calvin, Jr. 1991). However, no such increases in RVEDVI were observed in the current study albeit mean PAP and PA Ea rose by 30%. Under anesthetic conditions during which RV contractile function is well preserved, it may be difficult to determine the small changes in EDP and volume that are expected to occur consequent to

increases in afterload that do not exceed 200% of baseline (Fourie, Coetzee et al. 1992b; Fourie 1989). Furthermore, the RVEF catheter has at least a 10 to 15% variation in measurement of RV volume (Conrad 2001). Should afterload have increased further (Calvin, Jr. 1991; Sarnoff and Berglund 1954) or RV contractility be further depressed, it is most likely that the RV would have been forced to utilise its preload reserve in an attempt to generate stroke work (Coetzee, Fourie et al. 1987a).

Another important factor to take into account when considering the well-preserved ventricular function is that the subjects enrolled in the present study formed part of a select group of patients. Normal adult mean PAP, measured in the supine position, at rest, and while breathing air at sea level, has been described as being 14.3 ± 3 mm Hg (Marshall and Marshall 1997). From this observation, a mean PAP of more than 25 mm Hg will occur in less than 1% of the population. Marshall and Marshall therefore consider the definition of pulmonary hypertension to be a mean PAP of greater than or equal to 25 mm Hg (Marshall and Marshall 1997). Only one of 52 subjects in whom baseline PA pressure was measured in this study had a mean PAP pressure exceeding 25 mm Hg. The patient with the highest resting mean PAP (30 mm Hg) also had the lowest VO_2max (11.1 $ml.kg^{-1}.min^{-1}$) of any patient in the current study. A limited pulmonary vascular reserve would be unmasked by a limited ability of the RV to increase cardiac output in the face of severe rises in PA pressure on exercise (Okada, Ishii et al. 1996; Basson 1996; Sue and Wasserman 1991). This would be unmasked during preoperative exercise testing (Okada, Ishii et al. 1996). However, not all patients underwent preoperative exercise testing. If mean PAP is considered to be the product of PVR and cardiac output, a low cardiac output at rest may indicate a very limited pulmonary vascular reserve but still have resting pulmonary artery pressures that are high but do not qualify to be designated as “pulmonary hypertension” (Marshall and Marshall 1997; Okada, Ishii et al. 1996). Low resting cardiac outputs were not however observed during the awake step in the current study.

Preoperative exercise capacity was severely limited in 19% of the patients. In other words, 7 out of 36 patients in whom preoperative exercise capacity was measured had a VO_2max of less than 15 $ml.kg^{-1}.min^{-1}$. However, no relationship could be demonstrated between mean PAP measured before induction of anesthesia and preoperative exercise capacity as measured by VO_2max in this study (Table 3.5.10). An important factor pointed out by Marshall and Marshall is that in the presence of a diminished pulmonary vascular reserve, significant increases of PA pressure occur on exercise. The increases in PA pressure will lead to RV hypertrophy (RVH) (Stoltzfus 1997; Marshall and Marshall 1997; Okada, Ishii et al. 1996). Moderate amounts of RVH are difficult to diagnose without extensive cardiac investigations (Wiedemann and Matthay 1997) but the increase in stroke work induced by mild RVH would have facilitated coupling between the RV and its load intraoperatively (Marshall and Marshall 1997).

It is also noteworthy that the 3 subjects in the control group with a VO_2max of between 11 to 15 $ml.kg^{-1}.min^{-1}$ did not exhibit signs of RV dysfunction or failure during OLA. This implies that although VO_2max is in this low range, it should probably not be considered a contra-indication for patients to be subjected to OLA when a balanced anesthetic technique as used in the current study is employed and surgical resection (when done) is carefully considered with reference to prediction of how much pulmonary function will remain (Coetzee 2000; Basson 1996; Bolliger, Wyser et al. 1995; Bolliger, Jordan et al. 1995).

In summary with respect to RV performance during OLA (continued from previous summary on page 268)

1. The anesthetic technique used in the present study had a minimal effect on RV function immediately after induction of anesthesia. Nonetheless, LVSWI decreased during this step.
2. Sympathetic nervous system stimulation during surgical stimulation was not completely obtunded by the anesthetic technique employed in this study. As suggested by Cohen, the catecholamine release aids maintenance of the circulation during OLA (Cohen, Eisenkraft et al. 1988). The differential effect of the inhalation anesthetic agents on the ventricles, and the RV in particular, has threatened the integrity of the circulation in certain studies (Heerdt, Gandhi et al. 1998; Coetzee 1993). The use of a single anesthetic agent at high partial pressures or plasma concentrations may not provide optimal conditions for either the circulation or arterial oxygenation during OLA (Abe, Mashimo et al. 1998; Fourie, Coetzee et al. 1992b; Piene 1987; Piene and Sund 1982; Piene and Sund 1979)
3. Well-preserved LV function may be crucial for the transmission of blood via the pulmonary vasculature.
4. Above a preoperative VO_2max of 11 ml.kg^{-1}.min^{-1}, RV performance is well preserved during OLA.

4.4 Control group: oxygenation during OLA

4.4.1 Overview

One of the major concerns of anesthesiologists during OLA has been to maintain adequate arterial oxygenation (Table 4.4.1) (Slinger and Scott 1995; Barker, Clarke et al. 1993; Benumof 1991). This concern is seen by the cost of oxygenating patients (as judged by the alveolar-arterial oxygen tension difference, PaO_2/FiO_2 ratio, and the shunt fraction) in the current study increased during OLA compared to both the awake and two-lung anesthesia steps. The shunt fraction doubled to 36% during OLA compared with awake values. This increase in shunt fraction was accompanied by a 40% decrease in the P_aO_2/ F_iO_2 ratio and a 7 to 8 fold increase in the alveolar-arterial oxygen difference in the OLA step compared to the baseline awake step. The shunt fractions and indices of arterial oxygenation observed during OLA in the current study are comparable to those seen in other studies (Pagel, Fu et al. 1998; Cohen, Eisenkraft et al. 1988; Domino, Borowec et al. 1986; Katz, Laverne et al. 1982; Capan, Turndorf et al. 1980; Jarmakani, Nakazawa et al. 1976). The shunt equation calculates an *"as if"* shunt. In other words, the shunt equation calculates the shunt *assuming* that (*"as if"*) the depression of arterial PaO_2 is entirely due to the addition of mixed venous blood. The shunt equation does not consider the decrease in PaO_2 that results from the presence of low V/Q units (West 1985). However breathing 100% oxygen, as was used in this study, eliminates the contribution of low ventilation perfusion units to measurement of shunt because any V/Q unit that is not zero will fully saturate with oxygen (Moon and Camporesi 2000). Therefore, estimation of shunt fraction during the use of 100% oxygen accurately measures the actual degree of shunt present (Moon and Camporesi 2000; West 1985).

In the current study, in spite of the increase in shunt and cost of oxygenation, both arterial oxygen tension and saturation *increased* during OLA compared to when the patients were awake. This belies the fact that oxygenation is a problem during OLA as is usually reported (Slinger and Scott 1995; Barker, Clarke et al. 1993; Benumof 1991; Capan, Turndorf et al. 1990). This also underscores the power of the manoeuvres detailed below which were employed in this study to address oxygenation during OLA.

The incidence of hypoxia during one lung anesthesia		
Authors	Incidence of hypoxia %	* PaO_2 < 10.6 kPa ** PaO_2 < 13.3 kPa
Tarhan and Lundborg, 1970	35	*
Kerr, Smith et al, 1974	25	*
Das, Fenstermacher et al, 1970	40	**
Aalto, Heinonen et al, 1975	27	*
Flacke, Thompson et al, 1976	15	*
Capan, Turndorf et al, 1980	27	*
Katz, Laverne et al, 1982	30	*
Rees and Wansbrough, 1982	50	**

Table 4.4.1 Adapted from (Capan, Turndorf et al. 1990).

When discussing arterial oxygenation it is important to consider the following factors (Coetzee 1987):

1. Inspired oxygen concentration,
2. Alveolar ventilation. (1 and 2, and the prevailing barometric pressure of the atmosphere, determine the alveolar partial pressure of oxygen of ventilated alveoli),
3. Venous admixture,
4. Shunt fraction and,
5. The mixed venous oxygen tension in the light of the prevailing shunt fraction.

It would be useful to write the discussion regarding oxygenation in a circular fashion, as the various factors are interdependent on one another. A particular focus of the current study was to investigate the influence of right ventricular function on systemic oxygen delivery and consumption: Mixed venous oxygenation reflects the balance of systemic oxygen supply to oxygen demand (Marino 2003; Mark, Slaughter et al. 2000). In turn, P□O_2 will significantly influence arterial oxygenation in the presence of a large shunt (Amsel, Rodrigus et al. 1995; West 1985). Recent review articles on thoracic anesthesia have failed to consider the influence of mixed venous oxygen tension on arterial oxygenation during OLA (Benumof and Alfery 2000; Cohen 1995; Cohen 1995; Benumof 1991; Siegel and Brodsky 1991). Nonetheless, Benumof (Benumof 1986) and Capan and colleagues did address the issue in 1990 (Capan, Turndorf et al. 1990).

4.4.2 Control group: mixed venous oxygenation

Mixed venous saturation recorded when the subjects were awake was 74.9 ± 5.5%. These values fall within a range of values (68 to 77%) that are regarded as being normal for humans (Marino 2003). However, a clinically significant

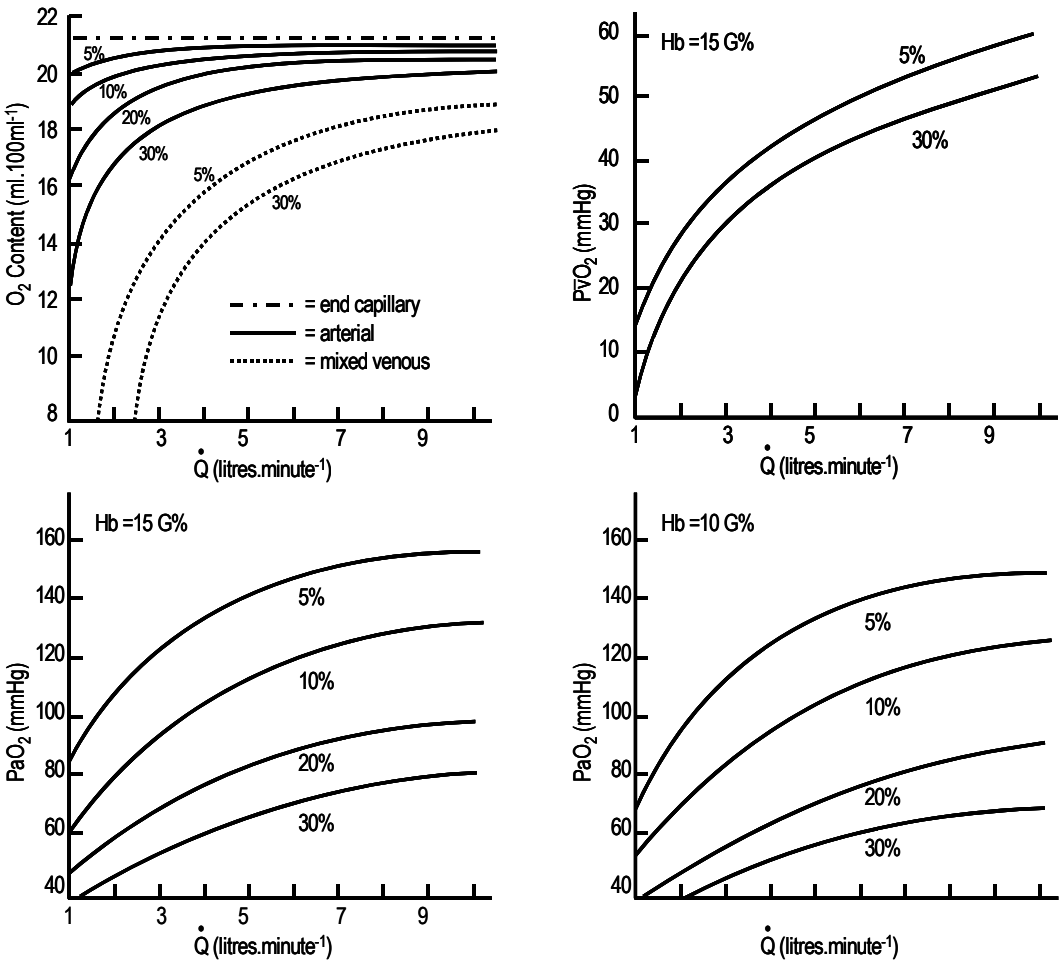


Figure 4.4.2.1 The theoretical relationships between cardiac output on mixed venous and arterial oxygenation in the presence of various shunt fractions. Redrawn from Kellman, Nunn et al, 1967.

rise in mixed venous oxygen tension and saturation was observed during both two and one lung anesthesia. This differs significantly from that observed in other studies (Zaune, Knarr et al. 1990; Thys, Cohen et al. 1988). This rise was so significant that it frequently approached levels that are considered respectable arterial oxygen tensions (average P□O_2 8.4 ± 1.8 kPa and S□O_2 87.2 ± 4.6 %) during all OLA steps. In fact, during OLA in the control group, 37% of measurements of venous saturation were greater than or equal to 90% and 46% of venous oxygen tensions exceeded 8 kPa. These rises mean that the relationship between P□O_2 and S□O_2 was now functioning on the flat part of the oxygen dissociation curve (ODC). The respiratory acidosis present during OLA would have increased the P_{50} and had the effect of shifting the oxygen dissociation curve to the right (figure 4.8.1). This rightward shift of the ODC during OLA would have increased the possibility that the relationship between venous oxygen tension and saturation was operating on the flat part of the oxygen dissociation curve (West 1985).

The Fick equation (Equation 4.4.1) can be re-arranged (Equations 4.4.2 and 4.4.3) to elucidate how venous oxygen content and saturation are influenced by cardiac output, oxygen consumption and arterial oxygen content (Marino 2003; Mark, Slaughter et al. 2000).

$VO_2 = CO\ (CaO_2 - C\square O_2)$ ..... Equation 4.4.1

$C\square O_2 = CaO_2 - VO_2/CO$ ..... Equation 4.4.2

$S\square O_2 = SaO_2 - (VO_2/(CO \times 1.36 \times [Hb]))$..... Equation 4.4.3

In the control group, arterial oxygen tension rose from an average of 11.2 ± 1.9 kPa while the patients were awake to 58.9 ± 8.8 kPa on initiation of anesthesia. PaO_2 varied between 32.5 ± 10.3 and 38.4 ± 17.3 kPa during OLA. However, because of the "flat" relationship between arterial oxygen saturation and tension at the high values at which these patients were functioning, the statistically significant rise in oxygen saturation between the awake and OLA steps had minimal clinical implications. Furthermore, the effect of this moderate rise in arterial saturation was offset by a decrease in hematocrit due to fluid administration. This is reflected by an 18% decrease in arterial oxygen content (CaO_2) measured after induction of anesthesia. CaO_2 remained at these levels throughout OLA except for the last step in the control group. Therefore, the reason for the increase in venous oxygenation was not an increase in CaO_2. Therefore, the mechanisms for the increase in $C\square O_2$ should be sought by considering oxygen consumption and cardiac output.

Cardiac output, normalized for body surface area, increased 35% on initiation of OLA. This was due to an increase in heart rate and not an increase in stroke volume. As discussed above, a temporal relationship existed between the increase in cardiac output and the surgical stimulation; the increase in cardiac output is most likely attributed to sympathetic nervous system activity secondary to surgical stimulation. The product of oxygen content and cardiac output determines tissue oxygen delivery. The net result of the increase in cardiac output and the small decrease in CaO_2 was a DO_2 during OLA that did not differ from baseline values. Therefore, the increases in $P\square O_2$ and $S\square O_2$ cannot be explained by an increase in cardiac output that resulted in a greater delivery of oxygen to the tissues.

The only remaining possibility for the increased $C\square O_2$ during OLA is that the oxygen consumption decreased during anesthesia. Compared with the awake state, oxygen consumption decreased by 45% during two-lung anesthesia and by up to 38% during OLA compared with awake controls. The oxygen extraction ratio (OER) and the arterial-venous oxygen content difference also decreased by approximately 40% after induction of anesthesia and during OLA. In other words, the decrease in oxygen consumption during anesthesia combined with an unchanged oxygen delivery was reflected by a significant decrease in the proportion of the delivered oxygen being extracted by the tissues.

Oxygen consumption in humans under nitrous oxide and fentanyl anesthesia has been reported to be 109 ± 16 $ml.min^{-1}.m^{-2}$ (Shibutani, Komatsu et al. 1983) and 110 to 130 $ml.min^{-1}.m^{-2}$ (Noe, Whitty et al. 1980). Albeit anesthesia techniques were not the same in these and the current study, these values for oxygen consumption appear to be greater than the 78 ± 13 to 98 ± 26 $ml.min^{-1}.m^{-2}$ observed in the current study. Carli and co-workers also demonstrated a 20% decrease in VO_2 at one MAC of both halothane and isoflurane in non-surgically stimulated patients (Carli, Ronzoni et al. 1993). Theye and Michenfelder previously demonstrated in dogs that inhalation anesthetic agents (halothane, isoflurane and enflurane) produce dose dependent decreases in whole body oxygen consumption (Theye and Michenfelder 1975). The decrease in oxygen consumption was maximal when the highest partial pressures of the inhalation anesthetic agent were administered, i.e. 29% decrease at 2,2 MAC enflurane, 27% at 2 MAC halothane and 22% at 2.3% isoflurane. Scheeren and colleagues studied sevoflurane and desflurane, in

addition to all the inhalation anesthetic agents investigated in the aforementioned studies (Scheeren, Schwarte et al. 1999). They observed similar 30% decreases in VO_2 at 2 MAC of all the inhalation anesthetic agents examined.

Theye and Michenfelder also demonstrated that inhalation anesthetic agents do not cause significant depression of sphlancnic, skeletal and renal oxygen consumption. The decrease in oxygen consumption that they observed was primarily due to a decrease in myocardial oxygen consumption because of a decrease in cardiac stroke work (lower MAP and cardiac output) (Theye and Michenfelder 1975). Michenfelder and Theye concurred with Mikat and co-workers (Mikat, Peters et al. 1984) that *"the inhalation anesthetic agents are not generalized metabolic depressants"* (Theye and Michenfelder 1975; Theye and Michenfelder 1975; Theye and Sessler 1967).

It is noteworthy that in the current study, oxygen consumption was decreased by up to 55% more than in other studies (Scheeren, Schwarte et al. 1999; Carli, Ronzoni et al. 1993; Mikat, Peters et al. 1984; Noe, Whitty et al. 1980; Theye and Michenfelder 1975). Nonetheless, the dose of inhalation anesthetic agent was less in the current study than in the aforementioned studies. The question may be posed as to whether other balanced anesthetic techniques comprising a combination of high dosages of opioid and relatively low dose inhalation anesthetic agent (as was used in our study), decrease oxygen consumption to a greater degree than that of an inhalation anesthetic agent administered as a lone drug? The answer to this question has not been widely studied. However, in a yet unpublished study entitled "Sevoflurane compared with halothane to supplement computer controlled sufentanil infusions during anesthesia for coronary artery bypass surgery," (Levin, Coetzer et al. 2002) significant decreases in oxygen consumption were found. This study provided anesthesia utilising a computer-controlled infusion of sufentanil at 2 $ng.ml^{-1}$ in addition to 0.35 MAC of either halothane or sevoflurane. This decrease in oxygen consumption occurred in spite of the differences between the current and the unpublished study. In the aforementioned study, both lungs were ventilated, and furthermore, the circulation was threatened by patient pathology (severe coronary artery disease), drug usage (beta adrenoreceptor blocking agents and/or phenylephrine). However, the relevant issue is that oxygen consumption decreased significantly in both these studies. The common thread was the use of balanced anesthesia that employed relatively high levels of opioid at constant blood concentration in combination with small dosages of inhalation anesthetic agent at concentrations that just exceeded MAC aware. Furthermore, in both studies, administration of anesthesia resulted in an improved efficacy of the circulation as judged by an increase in $P\square O_2$. The following hypotheses can therefore be generated. Firstly, that balanced anesthesia provides a greater margin of safety to patients in whom systemic and arterial oxygenation is threatened. Secondly, that many combinations of high dose opioid with low dose inhalation anesthetic agent provide similar benefits. Which combination and concentrations of these agents would provide the best safety margin in terms of the reduction of VO_2, is unknown at present. One concern is that prolonged infusions of opioid may result in a long context sensitive decrement time resulting in delayed recovery. Prolonged postoperative ventilation may be inappropriate after thoracic surgery. One solution to this problem is to utilise remifentanil in combination with one of the more insoluble inhalation anesthetic agents. The context sensitive half-life of remifentanil does not increase with time (Bailey, Egan et al. 2000). The hypothesis put forward is that remifentanil in combination with one of the more insoluble inhalation anesthetic agents will demonstrate similar beneficial reductions in oxygen consumption as other opioid-inhalation anesthetic agent combinations, without prolonging wakeup time.

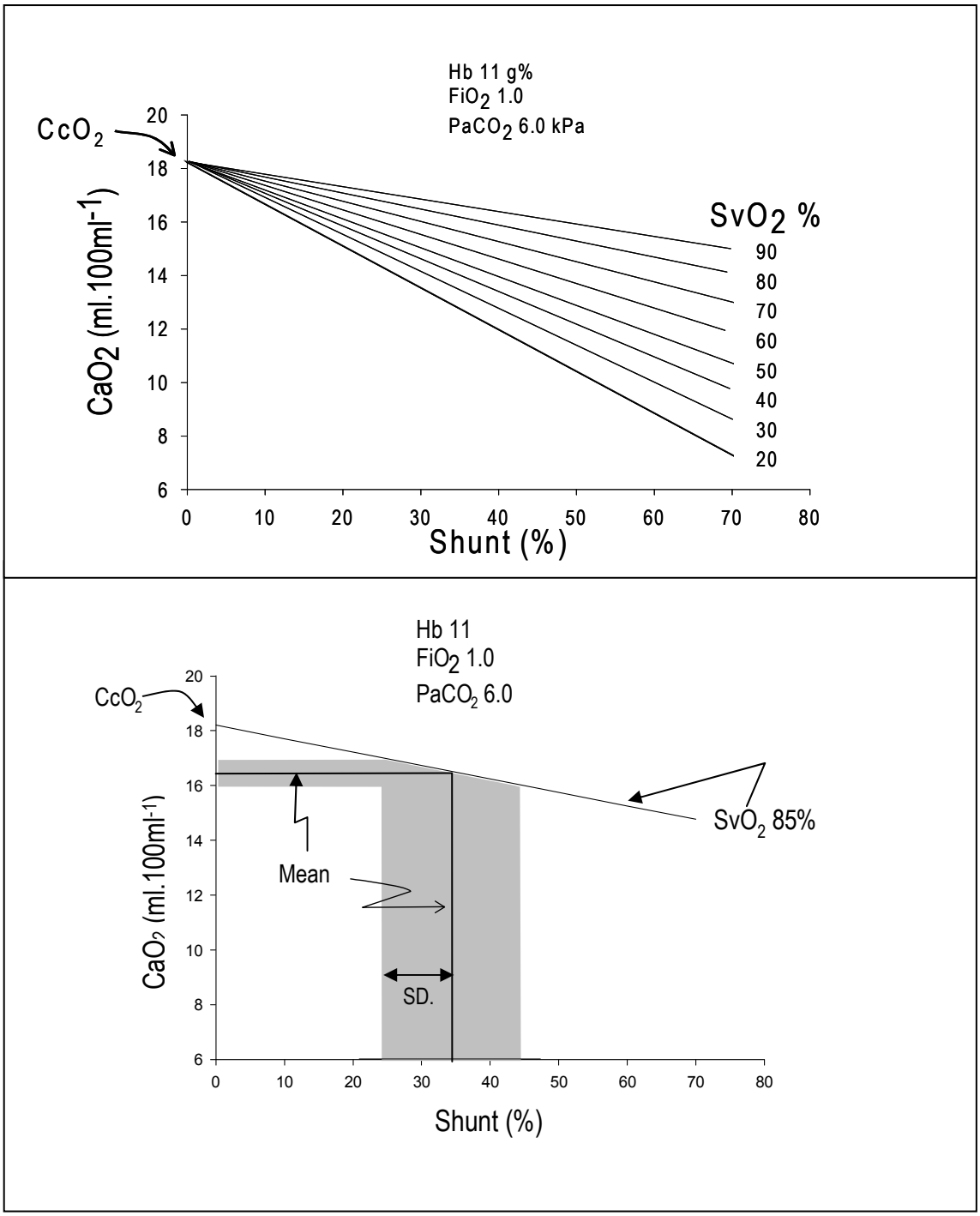


Figure 4.4.2.2. *The top diagram illustrates that the greater the venous oxygen saturation, the lesser the effect that this will have on arterial saturation at a particular shunt fraction, and vice versa. The above set of isosaturation lines are plotted assuming a constant cardiac output, hemoglobin concentration of 11g%, FiO_2 of 1.0, and $PaCO_2$ 6.0 kPa. These values are representative of the mean control group data during OLA in the current study. For each isosaturation line plot, the CaO_2 was calculated using equation 4.4.2.6 over a range of shunt fractions form 0 to 100% using Microsoft Excel®. The above set of relationships was then constructed using Sigmaplot® version 5, SPSS, USA. The concept used to construct these relationships was originally published by Coetzee in The Southern African Journal of Critical Care, 1987. The bottom diagram includes only values illustrative of the values observed during OLA in the control group. It appears as if the values for arterial oxygen content correspond with the values actually obtained in the study patients (Table 3.3.1.6)*

The influence of oxygen delivery and P□O_2 on arterial oxygenation in the presence of the significant shunt that occurs during OLA has been studied by Mathru et al. (Mathru, Dries et al. 1990), and Kelman and colleagues (Kelman, Nunn et al. 1967)

Kelman and colleagues theoretically "*explored the quantitative relationship between cardiac output and arterial PO_2 because … the admixture of venous blood with a lower oxygen content must inevitably lower the oxygen content of … arterial blood*" (Kelman, Nunn et al. 1967). For this purpose, they utilised a modified version of the Fick equation. Their formula was derived in the following way.

If the Fick equation, is solved for C□O_2, then

$$C\square O_2 = CaO_2 - VO_2/Qt \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 4.4.2.1}$$

If Equation 4.4.2.1 is inserted the following equation[#]

$$VO_2 = (Qt - Qs) \times (CcO_2 - C\square O_2) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 4.4.2.2}$$

Then

$$VO_2 = (Qt - Qs) \times (CcO_2 - CaO_2 + VO_2/Qt) \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 4.4.2.3}$$

This can be rearranged as:

$$CaO_2 = CcO_2 - \frac{VO_2\,(Qs/Qt)}{10[1-(Qs/Qt)]\,Qt} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation 4.4.2.4}^{\nabla}$$

To construct the graphs in figure 4.4.2.1, Kelman and colleagues assumed that VO_2 was 200 ml.min^{-1}, and remained

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[#] The origin of equation 4.4.2.2 can be deduced as follows:

$$CaO_2.Qt = CcO_2\,(Qt - Qs) + C\square O_2.Qs \ldots\ldots\ldots\ldots\ldots \quad \text{Equation a (West, Pulmonary physiology, Chapter5, page 53, 1985)}$$

Expanding equation a:

$$CaO_2.Qt = CcO_2.Qt - CcO_2.Qs + C\square O_2.Qs \ldots\ldots\ldots\ldots\ldots \quad \text{Equation b}$$

The Fick equation (West, 1985):

$$VO_2 = Qt\,(CaO_2 - C\square O_2) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation c}$$

Solving equation c for $CaO_2.Qt$:

$$CaO_2.Qt = VO_2 + Qt.\,C\square O_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad \text{Equation d}$$

Substituting equation d into equation a

$$VO_2 + Qt.\,C\square O_2 = CcO_2\,(Qt - Qs) + C\square O_2.Qs \ldots\ldots\ldots\ldots\ldots \quad \text{Equation e}$$

Simplifying equation e results in equation 4.4.2.2

$$VO_2 = (Qt - Qs) \times (CcO_2 - C\square O_2)$$

[∇] Note that the occurrence of the number "10" in Equation 4.4.2.4 is because oxygen content is normally expressed in units of ml per 100 ml of blood, whereas cardiac index is expressed in units of liters per minute.

constant as cardiac output changed. Hemoglobin concentration was assumed to be 15 g.100ml^{-1} of blood. Their results are reproduced graphically in figure 4.4.2.1. They concluded that moderate decreases in cardiac output, when combined with an increased shunt, resulted in striking decreases in venous oxygen tension with resultant decreases in arterial oxygen tension. Both of these effects will occur more rapidly when hemoglobin concentration declines to 10 g.100ml^{-1} because of a concomitant decrease in the oxygen content of blood. The differences between their theoretical study and the current one are that:

- Oxygen consumption in our anesthetised patients was lower than that assumed in their study,
- They did not consider shunt fractions of the magnitude seen during OLA and,
- Hemoglobin concentrations were approximately 11 g.100ml^{-1} in the present study.

To make their concepts more applicable to the current study, values representative of the control group during OLA were entered into a spreadsheet (Microsoft Excel®) and were modelled using Kelman and colleagues' formula (Equation 4.4.2.4). These graphs are reproduced in Figure 4.4.2.3. Data used to construct this graph reflected average results obtained in the control group of this study during OLA i.e. shunt 36.5%, oxygen consumption 95 ml.min^{-1}.m^{-2}, hematocrit 33.5% and CcO_2 17.5 ml.100ml^{-1}. A family of curves were obtained for various rates of oxygen consumption, representative of when the patients were awake, during two-lung anesthesia and at the extremes of what were seen during OLA. For illustrative purposes, CaO_2 is plotted against a wider range of cardiac indices than the 3.6 to 4.4 l.min^{-1}.m^{-2} ranges that was observed during OLA in the current study. The resultant relationships accurately agree with the arterial oxygen contents seen at the values of VO_2, cardiac indices, hematocrit and shunt fractions at which these patients were operating during OLA. It is apparent that the relationship between oxygen content and cardiac output is "flat" at the levels of oxygen consumed and at the levels of cardiac output that these patients were generating. Below the cardiac outputs seen in the current study and particularly when less than 3 l.min^{-1}.m^{-2}, arterial oxygen content and therefore oxygen saturation will decrease much more rapidly. The decrease in CaO_2 will be aggravated when VO_2 is increased. On the other hand, decreases in VO_2 shift this curve upward and to the left and provide a large safety net in terms of arterial oxygenation. Increasing hemoglobin concentrations has an even greater influence on shifting the relationship between cardiac output and CaO_2 to a more favourable position (see Figures 4.4.2.1 and 4.4.2.3). It can therefore be concluded that the decrease in oxygen consumption, that resulted in very high venous oxygen tensions and saturations, significantly improved arterial oxygenation in spite of the large 36% shunt observed during OLA. This is a seldom-reported consequence of adequate levels of balanced anesthesia and a decrease in VO_2 during OLA. Coetzee has published an approach to aid the understanding how mixed venous oxygenation influences arterial oxygenation in the presence of a shunt (Coetzee 1987). In this approach, (Figure 4.4.2.2), shunt and arterial oxygen content are linked by lines of equal venous saturations (venous isosaturation lines). For each isosaturation line plot, CaO_2 is calculated using equation 4.4.2.6 and plotted over a range of shunt fractions. The relationship elegantly demonstrates the influence of different levels of venous oxygen saturation on arterial oxygen content as shunt fraction increases. The relationship is derived using the following mathematical equations (West, Pulmonary physiology, Chapter 5, page 53, 1985):

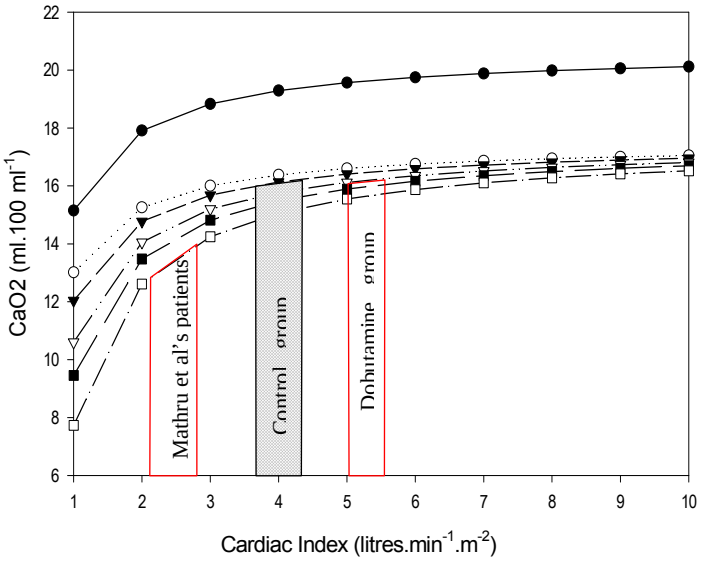

Figure 4.4.2.3 Influence of CO on arterial oxygenation for various levels of oxygen consumption during OLA using data gathered in the control group of the study. Hb = 11g.100 ml-1; pulmonary shunt = 36.5%; CcO2 17.5 ml.100 ml-1. The effect of an Hb of 15 g.100ml-1 at an oxygen consumption of 96 ml.min-1 is included for comparison. The patients in Mathru, Dries and colleagues 1990 study are also included for comparison.

- VO_2 96 ml.min-1.m^{-1}.m^{-2} at a [Hb] of 15 g.100ml^{-1}
- VO_2 76 ml.min^{-1}.m^{-2} as measured during two lung anesthesia in the current study
- VO_2 96 ml.min^{-1}.m^{-2} as measured during OLA at 35.5 ^{O}C
- VO_2 120 ml.min-1.m^{-1}.m^{-2} as mesured during OLA with administration of dobutamine
- VO_2 140 ml.min^{-1}.m^{-2} measured when patients in the current study were awake
- VO_2 170 ml.min^{-1}.m^{-1}.m^{-2} measured in the study by Mathru et al

$CaO_2.Qt = CcO_2 (Qt – Qs) + C\square O_2.Qs$ ..... Equation 4.4.2.5

Where

$CaO_2.Qt$ = amount of oxygen delivered to the tissues per minute,

$CcO_2 (Qt – Qs)$ = amount of oxygen emanating from the ventilated alveoli per minute and,

$C\square O_2.Qs$ = amount of oxygen passing via the shunt per minute.

Equation 4.4.2.5 may be described in the following conceptual way. The amount of arterial oxygen delivered to the tissues each minute is the sum of the quantities of oxygen contributed to the arterial circulation per minute firstly, by deoxygenated blood coursing via the shunt and secondly, by the blood that flowed past ventilated alveoli (assumed to be perfectly oxygenated). The amount of deoxygenated blood that flows via the shunt per minute is determined by the product of the volume of blood flowing via the shunt every minute (Qs) and the mixed venous oxygen content ($C\square O_2$) of that blood. It is important to note that both Qs and $C\square O_2$ determine the "size of a shunt" in terms of its effect on arterial oxygenation. Furthermore, the venous oxygen content is largely determined by the hemoglobin concentration and the venous oxygen saturation. The size of the shunt (Qs) itself may be influenced by the cardiac output. Therefore, at a particular hemoglobin concentration and cardiac output, a lesser amount of deoxygenated blood flows via a shunt (Qs) of a particular magnitude if the venous oxygen saturation increases. The implication of this is that higher venous oxygen saturation limits the "size of the shunt" in terms of its effect on depression of arterial oxygenation for a particular Qs/Qt ratio. Figure 4.2.2.2 was constructed using Equation 4.4.2.6 (a modification of Equation 4.4.2.5) and represents a graphic illustration of this concept.

If Equation 4.4.2.5 is expanded, it results in the following expression:

$CaO_2.Qt = CcO_2.Qt - CcO_2.Qs + C\square O_2.Qs$

The relationship between CaO_2 and shunt in figure 4.4.2.2 is obtained using equation 4.4.2.5 solved for CaO_2:

$CaO_2 = CcO_2 - Qs/Qt(CcO_2 - C\square O_2)$ ..... Equation 4.4.2.6

The implications of Equation 4.4.2.6 (as illustrated in Figure 4.4.2.2.) are

1. The equation describes a straight line of slope ($CcO_2 - C\square O_2$) and intercept CcO_2,
2. At a constant hemoglobin concentration, FiO_2 and alveolar ventilation, CcO_2 will be constant, and therefore the intercept on the CaO_2 axis will be constant.
3. As there is a linear relationship between $C\square O_2$ and $S\square O_2$ at a constant hemoglobin concentration, it is valid to label the lines in the figure using $S\square O_2$.
4. It also follows that, if CcO_2 and hemoglobin are constant, the slope of the line relating CaO_2 and shunt fraction depends entirely on the venous oxygen saturation. The lower the venous saturation, the greater the difference between CcO_2 and $C\square O_2$ and therefore the greater the negative slope of the line relating CaO_2 and shunt fraction.

The effect that the anesthetic technique has on the mixed venous oxygen tension is not often considered when investigating the effects of anesthesia during OLA (Pagel, Fu et al. 1998; Abe, Mashimo et al. 1998; Shimizu, Abe et al. 1997; Chen, Lee et al. 1996; Slinger and Scott 1995; Slinger and Scott 1995; Benumof, Augustine et al. 1987; Rogers and Benumof 1985; Bjertnaes, Mundal et al. 1980). Many studies have compared the effects of two inhalation anesthetic agents on HPV and arterial oxygenation during OLA. In order to do this they generally used relatively high partial pressures of a single anesthetic agent. However, these high partial pressures of inhalation anesthetic agent depress cardiac function without necessarily producing the same degree of decrease in oxygen consumption when using the balanced anesthesia technique employed in this study (Bailey, Egan et al. 2000). It is therefore not surprising that most studies report a decrease in P□O_2 during OLA that aggravates arterial hypoxemia in the presence of a large shunt. Furthermore, many studies focus attention on the inhibition of HPV by the inhalation anesthetic agent as being the major cause of worsening arterial hypoxemia during OLA (Abe, Shimizu et al. 1998; Pagel, Fu et al. 1998; Abe, Mashimo et al. 1998; Slinger and Scott 1995).

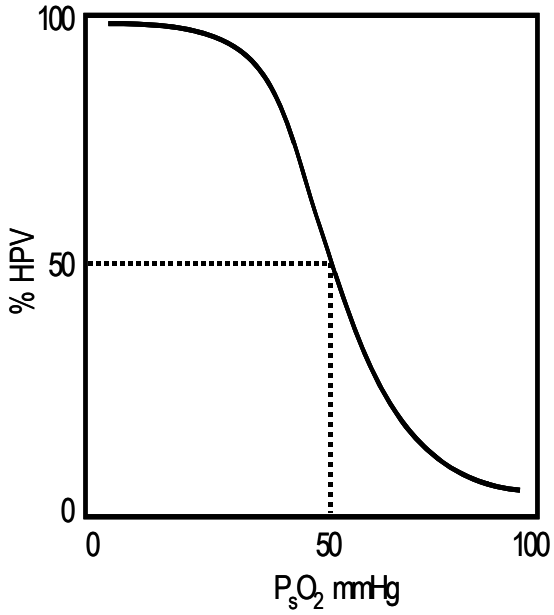

Figure 4.4.4.4 The sigmoid relationship between PsO_2 and HPV. Redrawn from Domino: Anesthetic modulation of vascular tone. Chapter 76 in Anesthesia: Biologic Foundations. Editors: Yakash et al, Lippincott – Raven publishers, Philadelphia, New York, USA, 1997.

A decrease in temperature of approximately 1^{O} Celsius was recorded in the epoch immediately after induction of anesthesia. This initial 1^{O} Celsius decrease in temperature is attributable to redistribution of heat between the periphery and the core (Sessler 2000; Kurz, Kurz et al. 1993; Parbrook, Davis et al. 1985). Whereas this redistribution cannot be prevented, further losses were counteracted by using a forced air warmer positioned over the lower half of the body to create an artificial microenvironment around the patient. Convection and radiation of heat to the environment account for a further 70% of the decreases in temperature (Parbrook, Davis et al. 1985). This decrease in temperature is relevant to this discussion because decreases in temperature result in a 7 to 8% decrease in VO_2 per degree Celsius (Schubert 1992). If delivery of oxygen is unchanged, this will contribute to increases in P□O_2 and therefore improve arterial oxygenation (Bacher, Illievich et al. 1997).

Bacher and colleagues' studied the influence of progressive hypothermia on VO_2 during anesthesia (Bacher, Illievich et al. 1997). They anesthetised their patients by administering a propofol infusion of 6 $mg.kg^{-1}.hr^{-1}$ and 5 $ug.kg^{-1}$ of fentanyl every 30 minutes. During anesthesia and surgery, at 35.5 ^{O}C, VO_2 was 100 ± 13 $ml.min^{-1}.m^{-2}$. This level of

VO_2 does not appear to be different to measurements made during OLA during the present investigation. At 32 ^{O}C, VO_2 was 77 ± 11 ml.min^{-1}.m^{-2}. Again this does not appear different from values observed in the anesthetised and non-surgically stimulated patients in the current study. However, the aim of decreasing temperature is to decrease VO_2; this would increase P□O_2 and benefit PaO_2 during OLA. In the Bacher study, albeit P□O_2 rose from 4.9 ± 0.3 kPa at 35.5 ^{O}C to 5.6 ± 0.9 kPa at 32 ^{O}C, it is surprising that these P□O_2 values are lower than those seen in the current study. The difference between the studies is not that hemoglobin concentrations differed from those in the current study. Neither does the difference rest therein that Bacher's patients were shivering (which would increase oxygen consumption) as vecuronium was repeatedly administered during hypothermia. The answer is that oxygen delivery at approximately 350 ml.min^{-1}.m^{-2} at 2.4 l. min^{-1}.m^{-2} is almost half of that in the current study. Thus, the comparison of the studies of Bacher and colleagues' and the present one emphasizes that if the benefits of a decrease in VO_2, associated with a decrease in temperature, are to be realized with a beneficial improvement in P□O_2, then DO_2 has to be optimised. The clinical implication of the aforementioned statement predominantly rests with the maintenance of a high-normal cardiac index and an adequate hemoglobin concentration.

An important consideration is that the large increase in P□O_2 observed in the current study would inhibit HPV (Capan, Turndorf et al. 1990; Benumof 1985; Katz, Laverne et al. 1982). The amount of HPV present at any time is governed by the partial pressure of oxygen (PsO_2) at the so-called "*sensor site*." The PsO_2 is governed by diffusion of oxygen from both the alveoli and the mixed venous blood (Benumof, Pirlo et al. 1981). The mathematical relationship for the oxygen tension at the sensor site (PsO_2 = P□O_2 $^{0.4}$ x $P_AO_2^{0.6}$) was originally determined by Marshall and Marshall (Marshall and Marshall 1997; Marshall and Marshall 1988). This relationship implies that the alveolar oxygen tension plays a more important role in determining PsO_2 than P□O_2. However, the rise in P□O_2 seen in this study will also have a significant influence on HPV.

Domino and colleagues used a dog model to study the influence of P□O_2 on HPV in the collapsed left lung of dogs. The dose response curve indicated that at a P□O_2 of 2.6 to 4 kPa, 50% of blood flow was diverted away from the atelectatic lung and HPV was abolished at a P□O_2 of more than 13.3 kPa (Domino, Wetstein et al. 1983). Thus, the raised mixed venous oxygen tension of 8.5 kPa during OLA would have resulted in significant inhibition of HPV in the NDL in the patients included in the current study.

The above influence of P□O_2 on HPV during OLA has to be contrasted with the classic approach to the relationship between HPV and cardiac output as described in figure 1.7.1.11. It essentially describes the mechanisms why inhalation anesthetic agents do not affect PaO2 during OLA. It is assumed that both cardiac output and P□O_2 decrease under anesthesia. This assumed decrease in P□O_2 potentiates HPV and thereby counterbalances the inhibition of HPV by the inhalation agent. The logic of this explanation is based on the assumption that anesthetic agents predominantly produce a depressant effect on the circulation. These assumptions do not apply to the effects of the anesthetic technique used in the current study that resulted in increases in PAP, cardiac output and P□O_2.

At least three other factors could have inhibited HPV during OLA in the current study. Firstly, Benumof has demonstrated that hypothermia progressively inhibits HPV while increases in temperature to 42 ^{o}C progressively potentiate HPV (Figure 4.4.4.5) (Benumof and Wahrenbrock 1977). However, Benumof and Wahrenbrock did not separate the effects of temperature and P□O_2 on HPV. Thus, the effects of temperature on HPV that were demonstrated by heating and cooling the dogs could possibly have been due to the effects of changes in oxygen consumption and the concomitant effects on P□O_2. Therefore, in the current study, it is difficult to separate the effects of the 1^{o} Celsius decrease in temperature on HPV from those of the increase in P□O_2. However, as similar decreases in temperature occurred in all patients, this is not an issue in the current study. Secondly, the end tidal isoflurane concentration of 0.5 kPa would have contributed to a further 6% inhibition of HPV (Domino 1997; Benumof 1986). Thirdly, the increase in PA pressure would have had a deleterious effect on HPV in the NDL (Malmkvist, Fletcher et al. 1989; Benumof and Wahrenbrock 1975). Therefore, for all the reasons discussed, it is doubtful whether, in this particular model, NDL HPV was of as much significance in determining oxygenation during OLA as is commonly suggested (Benumof 1986; Benumof 1985).

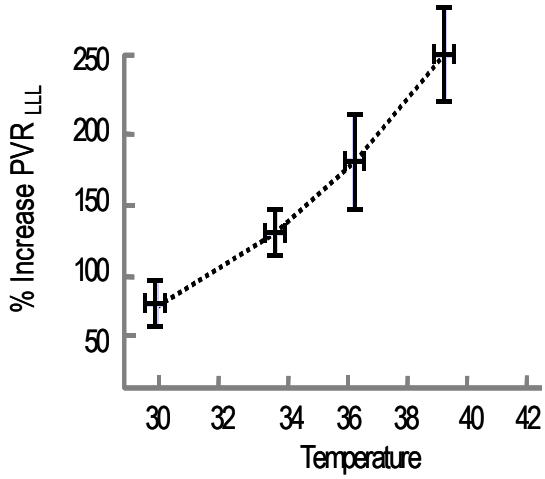

Figure 4.4.4.5 The effect of temperature on HPV. Redrawn from Benumof and Wahrenbrock, 1978.

In conclusion, the hypothesis that in the presence of the large shunt that occurs during OLA, the factors determining mixed venous oxygenation play an important role in determining arterial oxygenation, must be accepted (Amsel, Rodrigus et al. 1995; West 1985). Cohen and co-workers succinctly stated that the current approach to arterial oxygenation during OLA has been concentrated on minimizing DL PVR while maximizing PVR in the NDL. The aim of this approach is therefore to minimize NDL shunt (Cohen 1995; Cohen, Eisenkraft et al. 1988). The current approach to prevention of arterial hypoxemia during OLA includes using intravenous rather than inhalation anesthetics to minimize deleterious effects on NDL HPV, using pulmonary vasoconstrictors (almitrine, phenylephrine, prostaglandin $F_{2\alpha}$) to maximize NDL HPV and DL pulmonary vasodilators (nitric oxide) (Doering, Hanson et al. 1997; Capan, Turndorf et al. 1990). That the decrease in oxygen consumption induced predominantly by balanced anesthesia, but also by moderate hypothermia, aids arterial oxygenation during OLA, is a concept that is neglected in the literature and textbooks (Cohen 1995; Benumof 1991). The maintenance of the adequacy of delivery of oxygen must also be emphasized. The emphasis to date on minimizing the deleterious effects of inhalation anesthetic agents on HPV may well change in the light of the findings of the current study. Certain considerations now arise:

1. From Kelman and co-workers' data, it is apparent is that a cardiac output greater than 3 litres.min^{-1}.m^{-2} increase P□O_2, thereby improving arterial oxygenation (Kelman, Nunn et al. 1967). Will even greater increases in oxygen delivery with further rises in mixed venous oxygen tension progressively improve arterial oxygen tension during OLA? This issue will be addressed by the administration of dobutamine as

part of the current study.

2. Would further decreases in oxygen consumption that occur during more profound hypothermia result in even greater rises in P□O_2 benefit and further oxygenation during OLA?
3. What is the optimal and minimum oxygen carrying capacity (i.e. hemoglobin concentration) during OLA?
4. Do other balanced anesthetic techniques have similar beneficial effects on venous oxygen tension?
5. Will this balanced anesthesia technique benefit oxygenation during OLA in the supine position when gravity does not assist in minimizing shunt (Pinsky, Desmet et al. 1992)?
6. Are these principles of maintaining high levels of P□O_2 of importance during other clinical situations when right to left shunts occur? An example of an appropriate clinical situation would be a child with an intracardiac shunt due to congenital heart disease that is presented for corrective or palliative surgery.

4.4.3 Control group: Relationship between oxygen consumption and delivery

Once the patients were anesthetised, but before surgical stimulation occurred, both oxygen consumption and delivery decreased. However, oxygen delivery was always greater than the critical level under anesthesia of 330 $ml.min^{-1}.m^{-2}$ (Shibutani, Komatsu et al. 1983). Partial restoration of oxygen consumption and complete restoration of oxygen delivery to values observed before induction of anesthesia occurred after surgical incision. Furthermore, a significant relationship and linear correlation exists between DO_2I and VO_2I under anesthesia in the control group of the current study (Figure 3.5.6 and Table 3.5.2.). The implication of this relationship is that the more oxygen that is delivered to the tissues, the greater the amount of oxygen used. Does this constitute evidence that supply dependency existed in these patients under anesthesia? Supply dependency has been described before during anesthesia (Rock, Beattie et al. 1990). However, this dependency of oxygen consumption on oxygen demand during anesthesia is reported to be different in mechanism and much less in degree than the similar phenomenon that occurs during sepsis and systemic inflammatory response syndrome (Dantzker and Guiterrez 2002).

Theye and Michenfelder demonstrated that a large percentage of the decrease in total body oxygen consumption seen during anesthesia is attributable to the decrease in myocardial oxygen consumption (Theye and Michenfelder 1975; Theye and Sessler 1967). Coetzee et al's observations using various anesthetic agents that myocardial work decreases as depth of anesthesia is increased, is in agreement with Theye and Michenfelder's study (Coetzee, Fourie et al. 1987). Theye and Sessler similarly postulated that at least part of the supply dependency phenomenon represents changes in myocardial oxygen consumption that accompany anesthesia (Theye and Sessler 1967). Thus, it can be hypothesized that the decrease in total body VO_2 seen in these patients is due to the decrease in LV stroke work induced by anesthesia. This hypothesis cannot be directly tested in the current study, but the significant relationship that exists between LVSWI and whole body VO_2 may be considered as support for it (Table 3.5.2). However, examination of the relationship between LVSWI and VO_2 reveals only very weak relationships between the variables (Table 3.5.2). It is likely that two factors confound the ability to discover the aforementioned relationship:

1. Myocardial oxygen consumption is only a fraction of the total body VO_2. Thus, if myocardial oxygen consumption is not measured, it will be difficult to differentiate the increases directly attributed to myocardial oxygen consumption by studying whole body VO_2. This is indicated by the small 8% rise in VO_2 associated with increases in LVSWI, and,

2. Increases in sympathetic nervous system stimulation may increase *peripheral* oxygen consumption (Karzai, Lotte et al. 1996; Karzai, Gunnicker et al. 1996; Karzai, Gunnicker et al. 1994).

The relationship observed between VO_2 and LVSWI raises a question. Will the increase in oxygen consumption that accompanies the increase in oxygen delivery deleteriously affect P□O_2 and therefore arterial oxygenation during OLA? The answer is probably that because of the small (8%) increase in VO_2 that accompanies the rise in oxygen delivery, P□O_2 will not be much depressed. Furthermore, any increase in VO_2 that accompanies an increase in LVSWI will start from a low baseline. It is also likely that any increase in LVSWI and therefore oxygen consumption will be more than compensated for by a greater increase in cardiac output. This will maintain the VO_2/DO_2 relationship with minimal effect on venous and therefore arterial oxygenation.

4.5 Ventilation during OLA

4.5.1 Ventilation during OLA: The maintenance of DL volume

OLA in the LDP is reported to result in a decrease in DL volume. This decrease in DL volume after induction of anesthesia exceeds that which occurs in the supine position when both lungs are being ventilated (Benumof and

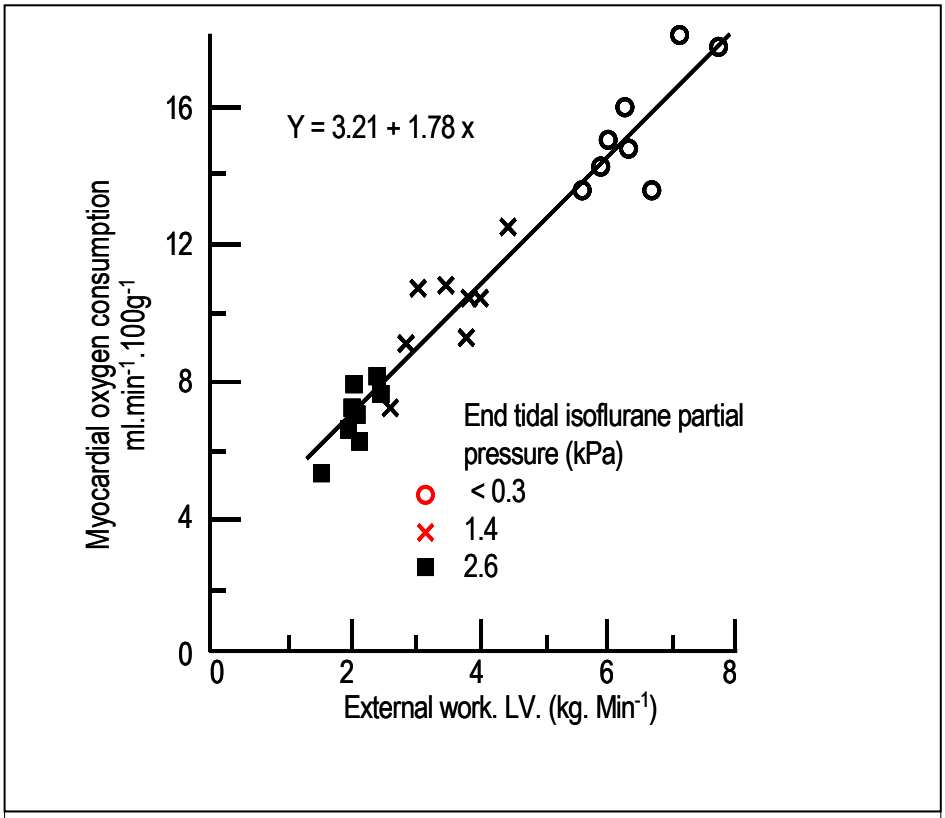

Figure 4.4.3.1 In previous work, Theye and Michenfelder showed that one of the main reasons for the decrease in systemic oxygen consumption under anesthesia is the decrease in LV work. In this graph, they demonstrate that it is not the partial pressure of isoflurane per se that is related to the myocardial oxygen consumption. However, myocardial oxygen consumption is directly related to left ventricular work. Redrawn from Theye and Michenfelder, 1975.

Alfery 2000; Cohen 1995; Siegel and Brodsky 1991; Klingstedt, Hedenstierna et al. 1990). The implication is that low V/Q ratios will develop in the DL. This decrease in lung volume will therefore contribute to arterial hypoxia during OLA (Hedenstierna 1998). The mechanisms causing this reduction in lung volume are attributed not only to DL compression by mediastinal weight and abdominal contents, but also to the presence of pre-existing lung disease, and the use of high concentrations of oxygen intraoperatively (Benumof and Alfery 2000; Cohen 1995; Benumof 1991; Siegel and Brodsky 1991; Capan, Turndorf et al. 1990). Splinting of the chest wall also contributes to the 41.9% lower static DL compliance described during OLA in the LDP (Szegedi, Bardoczky et al. 1997).

To maintain DL volume during OLA, most textbooks encourage DL ventilation with tidal volumes of 10 to 15 ml.kg^{-1} (Cohen 2001; Szegedi 2001; Cohen 1995; Benumof 1991). In the current study however, tidal volumes of only 6 to 7 ml.kg^{-1} were employed during OLA. The reasons why the decision was made to employ smaller tidal volumes and disregard the basis of these aforementioned recommendations, during this study needs to be discussed.

Research has been published indicating that the use of larger tidal volumes improves oxygenation during OLA (Katz, Laverne et al. 1982; Flacke, Thompson et al. 1976; Kerr, Smith et al. 1974; Khanam and Branthwaite 1973). Katz and his colleagues demonstrated that ventilation of the DL with larger tidal volumes (7 vs. 16 ml.kg^{-1}, i.e. 8 versus 16% of lung volume) during OLA improved both lung compliance and PaO_2 and was accompanied by beneficial decreases in shunt fraction from 39 ± 2 to 35 ± 2% ($p < 0.01$) (Katz, Laverne et al. 1982). An earlier study by Kerr and colleagues demonstrated that maintaining the same tidal volume (10–15 ml.kg^{-1}) during OLA as was used during two-lung anesthesia prevented the progressive 10% increase in shunt seen when lower (unspecified) tidal volumes were used (Kerr, Smith et al. 1974). Both these papers suggested that the reason oxygenation was better when greater tidal volumes were employed during OLA, was because of recruitment of DL atelectatic areas. A contrary view was however expressed by Khanam and Branthwaite who determined that smaller tidal volumes provided optimal arterial oxygenation and carbon dioxide tensions during OLA (Khanam and Branthwaite 1973). They first conducted a pilot study in which a smaller tidal volume of 7 ml.kg^{-1} at a rate of 20 breaths per minute was found to be "optimal" during OLA as judged by a *$PaCO_2$* of 4.0 to 5.3 kPa (Khanam and Branthwaite 1973). In their study, they showed that deviation from a tidal volume of 7 ml.kg^{-1} to one of either 5 or 9 ml.kg^{-1}, decreased arterial oxygenation (Khanam and Branthwaite 1973). However, both Cohen and Benumof's textbooks and even an excellent article by Capan and associates, all quote an article by Flacke and colleagues as being the reason they recommend DL tidal volumes of 10 to 12 ml.kg^{-1} during OLA. They both suggest that this is the midpoint between extremes of tidal volume not affecting arterial

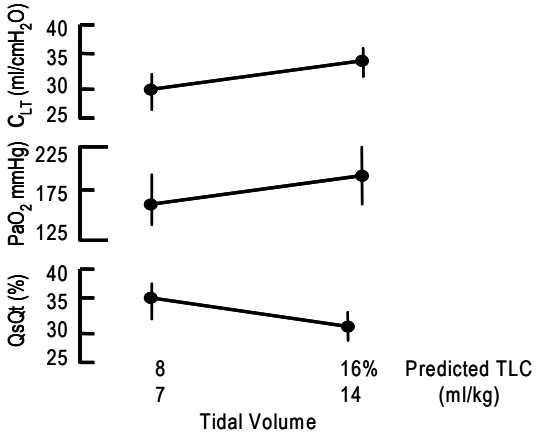

Figure 4.5.1 *The advantage of larger tidal volumes on lung mechanics and oxygenation during OLA is illustrated in this diagram reproduced from Katz, Laverne et al, 1982. At the larger tidal volume, all values are more favorable ($p < 0.05$, $n = 16$).*

oxygenation during OLA in the Flacke study (Cohen 1995; Benumof 1991; Capan, Turndorf et al. 1990; Flacke, Thompson et al. 1976). Scrutiny of the Flacke study indicates that part of their aims were to compare blood gases and shunt fraction when tidal volumes of 15 $ml.kg^{-1}$ and 8 $ml.kg^{-1}$ were used during one lung ventilation (Flacke, Thompson et al. 1976). However, the conclusion that the Flacke paper reached was that PaO_2 during one-lung ventilation was directly related to patients' preoperative oxygen tensions. They could demonstrate no relationship between PaO_2 and tidal volume. What they did recommend, however, in the light of the disparate results of tidal volume on PaO_2, was that an F_IO_2 of 1.0 should be used during one-lung ventilation.

Does this article by Flacke and colleagues really provide a solid foundation on which to base ventilation strategies for the majority of patients undergoing OLA? Surely Katz and colleagues, and Kerr and colleagues and others (Inomata, Nishikawa et al. 1997; Cohen and Eisenkraft 1996; Katz, Laverne et al. 1982; Kerr, Smith et al. 1974) have validly demonstrated that optimisation of DL FRC using larger tidal volumes minimizes PVR, decreases venous admixture in the DL and shunt to the NDL with optimisation of arterial oxygenation. The validity of basing ventilatory recommendations on the Flacke study is undermined by the observation made by these authors themselves. The abstract of this paper states that "*When V_T was reduced, patients who had had low oxygen tensions (< 150 mm Hg) at the higher volume, showed an increase in PaO_2, and conversely. Shunts changed accordingly*." This observation implies that the use of a greater tidal volume improves a low DL FRC and thereby arterial oxygenation, whereas patients with a well-maintained or even high DL FRC are deleteriously affected by higher tidal volumes during OLA (Flacke, Thompson et al. 1976). This concurs with observations made in an interesting study conducted by Cohen (Cohen, Thys et al. 1985b). He demonstrated that a select group of patients who were hypoxic during OLA, benefited by application of PEEP to the DL. Those patients who had a well-maintained PaO_2, however, did not demonstrate an increase in oxygenation during DL PEEP (Cohen, Thys et al. 1985b). This paper suggested that patients with a low DL volume had their DL volumes increased by 10 cm H_2O PEEP. Therefore, rather than the aim of a specific tidal volume or $PaCO_2$ level, (Benumof and Alfery 2000; Cohen 1995), it appears a more important consideration is maintaining a relatively normal dependent lung volume.

While the aforementioned discussion serves as justification for utilizing larger tidal volumes during OLA, it raises another question. Does the use of smaller tidal volumes during OLA as employed in the current study, lead to decreases in DL volume and, with time, worsening hypoxia during OLA (Benumof 1991; Capan, Turndorf et al. 1990; Flacke, Thompson et al. 1976; Kerr, Smith et al. 1974; Khanam and Branthwaite 1973; Das, Fenstermacher et al. 1970; Newnan, Finer et al. 1961)? In the current study, unlike other studies (Kerr, Smith et al. 1974; Das, Fenstermacher et al. 1970), no evidence of progressively decreasing arterial oxygenation became apparent as OLA progressed. This observation is a further justification to raise questions about the literature demonstrating that large tidal volumes are needed to maintain DL volume. The question why these parameters did not deteriorate during OLA with the use of low tidal volumes is commented upon in the PEEP section of this discussion.

4.5.2 Ventilation during OLA: avoidance of volotrauma

Another issue that may justify the use of smaller tidal volumes is the recent recognition that certain ventilatory strategies used in the ICU (The Acute Respiratory Distress Syndrome Network Study 2000; Amato, Barbas et al. 1998) may be harmful to the lung parenchyma (Slinger 1999; Williams, Evans et al. 1996; Quinlan and Buffington 1993). Furthermore, volotrauma has recently been recognized as a factor determining morbidity and even mortality

during OLA (Connery, Deignan et al. 1999; Conacher 1998; Myles, Madder et al. 1995; Myles and Weeks 1992). Post pneumonectomy pulmonary edema (PPE) occurs in 4 to 5% of patients and carries with it a high (50 to 80%) mortality. According to both Williams et al. (Williams, Evans et al. 1996) and Alvarez and co-workers (Alvarez, Bairstow et al. 1998), PPE presents as acute respiratory distress after lung resection. Progressive and refractory hypoxemia is followed by infiltrates on chest roentgenology. The causes originally associated with PPE were fluid overload and right pneumonectomy. These causes have recently become contentious as the main etiological factor. As Alvarez et al. state, "*there must be more to the answer of the PPE puzzle than withholding fluids*" (Slinger 1999; Alvarez, Bairstow et al. 1998; Slinger 1995). It appears that this condition is histologically and clinically indistinguishable from ALI with its hallmark of altered capillary permeability (Slinger 1999; Alvarez, Bairstow et al. 1998; Williams, Evans et al. 1996; Marini, Culver et al. 1985). The suggested etiological reasons are multiple (Slinger 1999; Williams, Evans et al. 1996; Slinger 1995; Slinger 1995; Eger 1994; Waller and Turner 1989; Marini, Culver et al. 1985). However, volotrauma is at present considered to play a key role in the etiology of PPE and ALI after OLA. The importance of volotrauma as an etiological factor lies therein that the anesthesiologist may be to blame by applying excessive tidal volumes or permitting the development of excessive levels of intrinsic PEEP during OLA (Slinger 1999).

Albeit the underlying pathologies are not the same, Myles suggests that the Acute Respiratory Distress Syndrome Network (ARDSnet) study may be of relevance for patients undergoing OLA that have pulmonary disease (Myles 2001). In the ARDSnet study, patients with acute lung injury who were ventilated with lower tidal volumes (6.2 ± 0.8 vs. 11.8 ± 0.8 $ml.kg^{-1}$; $p < 0.001$) and lower ***plateau*** airway pressures (25 ± 6 vs. 33 ± 8 cm H_2O; $p < 0.001$) had a lower mortality (31.0 vs. 39.8%; $p < 0.007$) and spent fewer days on a ventilator (The Acute Respiratory Distress Syndrome Network Study 2000). Support for Myles's suggestion, and of more relevance to the OLA situation, comes from a study by van der Werff and colleagues (van der Werff, van der Houwen et al. 1997). In 35 patients subjected to pneumonectomy, 11 developed respiratory distress and radiographic infiltrates. In all 11 patients, peak inspiratory pressures of more than 40 cm H_2O were used during OLA (van der Werff, van der Houwen et al. 1997).

Szegedi and colleagues demonstrated that plateau pressures (the correct pulmonary distending pressure) are only 70% of peak airway pressures during OLA (Szegedi, Bardoczky et al. 1997). (The difference between peak and plateau pressures can be understood if the resistance presented to the ventilator by the endotracheal tube and the patient's airways are taken into account). Considering both Van der Werff and Szegedi and colleagues' studies, Slinger suggested that it is advisable to limit plateau pressures to 25 cm H_2O and peak pressures to 35 cm H_2O to avoid lung damage during OLA (Slinger 1999; Szegedi, Bardoczky et al. 1997). Attention must be drawn to the fact that that transpulmonary pressure *per se* is not the major etiological factor causing trauma. Administering large tidal volumes during IPPV at low airway pressures is more damaging than IPPV at high airway pressures and normal tidal volumes in animals with their chests' bound (Slinger 1999; Hachenberg and Rettig 1998). Therefore although the current evidence points to the limitation of volume rather than the limitation of pressure to prevent lung damage, the importance of excessive inflation pressures lies therein that it may herald the use of excessive tidal volumes.

While there are concerns that utilizing tidal volumes of less than 8 $ml.kg^{-1}$ can have deleterious effects on DL volume (Cohen 2001), in the current study DL tidal volumes were limited to between 5.7 ± 1.4 and 6.7 ± 2.1 $ml.kg^{-1}$ (Tables

3.3.1.1, 3.3.2.1 and 3.3.3.1). Using these tidal volumes, rises in peak airway pressures were limited to between 25 ± 5.5 and 29 ± 5.4 cm H_2O during OLA except when extrinsic PEEP was applied [1] (Tables 3.3.1.3, 3.3.2.3 and 3.3.3.3). These tidal volumes and peak inspiratory pressures fall within the recommended ranges suggested to avoid the risk of volotrauma both during OLV and in patients with ALI (The Acute Respiratory Distress Syndrome Network Study 2000; Slinger 1999). Measurement of plateau airway pressures was not possible using the ventilating system currently available in the theatre. Plateau pressures are a better indication of transpulmonary distending pressures than the peak pressure used in this study (Moon and Camporesi 2000; Szegedi, Bardoczky et al. 1997). Using the principle described by Szegedi that only 70% of peak airway pressure is transmitted to the parenchyma, the plateau pressures were most likely within the aforementioned safe range recommended by Slinger (Slinger 1999).

One other consequence of using lower tidal volumes during OLA is that there is a significant negative relationship between cardiac index and plateau inspiratory pressures (Figure 1.7.2.2) (Aalto-Setala, Heinonen et al. 1975). In the current study, the avoidance of using large tidal volumes and excessive plateau airway pressures prevented decreases in cardiac output. Avoidance of this cause of a decrease in cardiac output is important in the light of the relationship between cardiac index and CaO_2 seen in the current study.

4.5.3 Ventilation during OLA: permissive hypercapnia

Currently, most authorities recommend titration of alveolar ventilation to a particular carbon dioxide tension during OLA (Benumof and Alfery 2000; Cohen 1995; Benumof 1991). However, blindly applying this strategy may cause damage to the lung if excessively high tidal volumes and respiratory rates are used. The problem is that volotrauma may be caused by either the excessive tidal volume and/or air trapping that occurs during OLV as expiratory time decreases (see PEEP section). Therefore, an aspect of a protective ventilation strategy during OLA involves avoiding titration of alveolar ventilation to a particular carbon dioxide tension (Morisaki, Serita et al. 1999; Tuxen 1994; Quinlan and Buffington 1993; Myles and Weeks 1992). As a consequence, a progressively increasing hypercarbia and respiratory acidosis was seen in the current study.

The highest $PaCO_2$ levels (6.9 ± 1.1 kPa) occurred in the last control group steps. A consequence of this was a decrease in pH to 7.3 ± 0.07 in the last steps of the control group. This pH was not due to a decrease in serum bicarbonate levels, as they remained unchanged from baseline in both the control and dobutamine groups (Figure 3.5.9). Base excess decreased as time progressed from 1.7 to – 0.2 $mmol.l^{-1}$ (control group), 2.7 to – 1.2 $mmol.l^{-1}$ (dobutamine group) and 1.2 to – 0.5 $mmol.l^{-1}$ (PEEP group). This statistical difference occurs because the sample size was large enough and contains data with little scatter. It is considered however of no clinical consequence.

The possible influence of this moderate respiratory acidosis on cardiac function is relevant to the current study (Morisaki, Serita et al. 1999; Quinlan and Buffington 1993). On the one hand, an acidosis of this degree could impair ventricular performance due to myocardial depression and/or the development of pulmonary hypertension (Solaro, Lee et al. 1988; Steinhart, Permutt et al. 1983). On the other hand, the increase in carbon dioxide tension may induce mild sympathetic nervous system stimulation and vasodilatation and improve cardiac output (Walley, Lewis et al. 1990). It is also important to consider the venous carbon dioxide tensions as this rapidly diffuses intracellularly, decreases tissue pH, and has been related to depression of cardiac function (Morisaki, Serita et al. 1999).

Nonetheless, no significant relationships between $PaCO_2$ and MAP, LVSWI, SVR, VO_2, characteristic impedance or stroke index were demonstrable. Furthermore, albeit statistically significant correlations do exist between $PaCO_2$ and cardiac index, heart rate, PVR and RVSWI, the strength of the relationships between these variables is weak and clinically insignificant (Table 3.5.4). One of the "stronger" associations noted is that 26% of the increases in both oxygen delivery and mean PAP is associated with the increase in $PaCO_2$. Therefore, as hypercarbia increases, it is possible that sympathetic nervous system stimulation induced by the increased carbon dioxide tension, accounts for a degree of the increase in oxygen delivery. However, a significant correlation does not imply a cause, only an association. Two variables may be related via their association with a third variable (Van der Linden, Schmartz et al. 2000). As was discussed earlier, the initiation of OLA coincided with the initiation of the surgical stimulus. Surgical stimulation may have resulted in an increase in sympathetic nervous system activity that was heralded by an increase in heart rate. Is it possible to separate the relative roles of surgical stimulation and hypercarbia on the increase in heart rate, cardiac index, and oxygen delivery during OLA? On studying the relationships between various factors, hypercarbia can only be associated with a small and clinically insignificant percentage (16 and 8%) of the increases in heart rate and cardiac index respectively. On the other hand, the increase in heart rate accounts for 30% of the increase in cardiac index. Therefore, the most probable conclusion is that the sympathetic nervous system stimulation associated with the surgical insult played the more important role in determining the increase in cardiac index with hypercarbia playing a lesser role in this process.

The other side of the coin is that no evidence of compromise of either left or right ventricular function exists nor was any significant degree of pulmonary vasoconstriction or systemic vasodilatation associated with the moderate respiratory acidosis that was permitted during OLA. The implication is that in this group of patients, hypercarbia to these levels was a safe event with respect to cardiac function. Hypercarbia may even have stimulated heart rate and cardiac output. Permissive hypercapnia has long been employed in the ICU to limit volotrauma during ventilation of patients with ALI and bronchospasm and also those with severe loss of elastic recoil during both two and one lung ventilation (Connery, Deignan et al. 1999; Morisaki, Serita et al. 1999; Conacher 1998; Myles, Madder et al. 1995; Myles, Madder et al. 1995; Tuxen 1994; Quinlan and Buffington 1993). Albeit permissive hypercapnia has been advocated during OLA, no studies have described the effects of moderate hypercapnia on hemodynamics during OLA.

The advantages of permissive hypercarbia during OLA are the limitation or prevention of air trapping and concomitant increases in FRC. Avoidance of air trapping will prevent the deleterious consequences of a decrease in venous return and an increase in RV afterload, which may result in severe hypotension or even cardiac arrest (Connery, Deignan et al. 1999; Conacher 1998; Myles, Madder et al. 1995). Tuxen describes that in severe airflow limitation due to asthma, an intrathoracic gas volume at the end of inspiration of less than 20 $ml.kg^{-1}$ reduces the risk of both hypotension and volotrauma (Tuxen 1994). As discussed in the literature review, the smaller the rise in airway pressure during OLA, the fewer deleterious effects that ventilation has on cardiac output. Therefore, smaller tidal volumes are associated for many reasons with a better cardiac output, as well as improved mixed venous and arterial oxygenation during OLA.

These beneficial effects must be balanced against the myocardial depression seen in experimental models when hypercarbia is induced (Solaro, Lee et al. 1988). The acidosis induced by the increase in carbon dioxide tension is suggested to be the major problem (Walley, Lewis et al. 1990; Solaro, Lee et al. 1988). Solaro and colleagues have suggested that the myocardial depression seen during hypercarbia is a result of the antagonism of calcium ion fluxes by the excess of hydrogen ions (Solaro, Lee et al. 1988). Because carbon dioxide readily diffuses intracellularly, it may result in the rapid onset of severe intracellular acidosis and myocardial cellular dysfunction (Walley, Lewis et al. 1990). Levels of respiratory acidosis slightly greater than in the current study ($PaCO_2$ 12 kPa and pH 7.09) have been shown to decrease end-systolic elastance by 20% in a dog model (Walley, Lewis et al. 1990). Furthermore, isolated strips of ventricular muscle demonstrated a 70% decrease in developed tension when exposed to a pH of 6.9 that was purely the result of hypercarbia (Solaro, Lee et al. 1988). The levels of hypercarbia and acidosis in these studies were greater than in the current study. It is of concern that during thoracic anesthesia, deleterious effects on canine RV function were observed at levels of $PaCO_2$ and pH ($PaCO_2$ 6.5 and pH 7.27) similar to those in the current study. The RV dysfunction was demonstrated by a fourfold increase in RV filling pressures in right ventricles facing an increase in afterload (Quinlan and Buffington 1993; Rose, Van Benthuysen et al. 1983).

It is remarkable however, that although myocardial depression was seen in the abovementioned dog model, cardiac output actually increased (Walley, Lewis et al. 1990). This was because hypercarbia induced an increase in preload, a decrease in afterload and catecholamine release. This underscores the divergent effects that respiratory acidosis has on circulatory function. One of the main factors underlying the increase in cardiac output is that respiratory acidosis does not inhibit the ventricular response to beta-adrenoreceptor agonists (Walley, Lewis et al. 1990; Steinhart, Permutt et al. 1983). In fact, Steinhart and colleagues demonstrated that B-adrenergic stimulation prevented cardiac failure associated with severe hypercarbia in a dog model ($PaCO_2$ 66 kPa and pH 6.39) (Steinhart, Permutt et al. 1983). This observation is supported by a report by Morisaki and colleagues (Morisaki, Serita et al. 1999). They retrospectively reviewed the records of patients with severe COPD during OLA and assessed the implications of permissive hypercapnia of a much greater degree than what was permitted in the current study. Mean $PaCO_2$ was 13.0 ± 3.0 kPa. All of the patients in Morisaki et al's study required inotropic support with 3 to 5 $ug.kg^{-1}.min^{-1}$ of dopamine and intermittent boluses of phenylephrine to maintain the circulation. Therefore, there appears to be a difference between the consequences of these higher carbon dioxide tensions in Morisaki's study and the lack of consequence of moderate hypercarbia in the current study. This lack of consequence supports the tolerance of moderate levels of respiratory acidosis in thoracic surgery.

Hypoxemia is a potential concern during OLA in which hypercapnia is permitted. Hypercarbia facilitates HPV (Benumof, Mathers et al. 1976), and avoids DL dynamic hyperinflation that would increase diversion of blood flow via the NDL shunt (Ishibe, Shiokawa et al. 1996). This will offset the deleterious effects of hypoventilation on alveolar and arterial oxygen tensions. Furthermore, utilizing high concentrations of oxygen while employing alveolar hypoventilation will result in the maintenance of an adequate alveolar oxygen tension. The simplified alveolar gas equation is $P_AO_2 = P_B\text{-}PH_2O - PaCO_2/RQ$. If RQ is 0.8, then for every kPa increase in $PaCO_2$, there is a 1.25 fold decrease in P_AO_2 (Coetzee 1987). However, the corollary of this statement is that increasing the inspired oxygen concentrations easily compensates for decreases in PAO2 due to hypoventilation. This benefit will apply even to carbon dioxide concentrations at the extremes of physiological abnormality.

4.5.4 Inspired oxygen concentration: dependent lung, all groups

An additional advantage of using higher concentrations of oxygen is that the movement of gas across the blood gas barrier is dependent on the partial pressure gradient of oxygen between the alveolus and pulmonary capillary (West 1985). The higher the alveolar oxygen partial pressure, the greater the transfer rate. The normal difference at the beginning of the capillary is approximately 8 kPa (West 1985). Increasing the fraction of inspired oxygen to 1 would have resulted in a DL alveolar oxygen tension of 95.03 kPa during OLA. The lowest P□O_2 during one lung anesthesia in this study was 8.1 ± 0.8 kPa. Therefore the gradient that resulted between the alveolus and pulmonary capillary would have been at least 87 kPa in the current study. This almost 10 fold rise in the gradient compared with breathing air, would have increased the rate of oxygen transfer across the alveolar capillary membrane (West 1985). This adds an additional compensatory mechanism for hypoventilation. For the short periods of time that these high concentrations of oxygen are used, oxygen toxicity is not considered a problem (Nunn 1987). Dantzker and colleagues theoretically determined the critical V/Q ratio of an alveolus to be 0.08 to 0.1 when using 100% oxygen (Dantzker, Wagner et al. 2002). This F_iO_2 has been shown to result in absorption atelectasis with a consequent 10% decrease in FRC (Baker, McGinn et al. 1993). This will potentially contribute to an increase in shunt fraction (West 1985). However, in the current study no increase in shunt fraction was observed as OLA progressed. This may be because intrinsic PEEP maintained patency of some of the lower V/Q units (Klingstedt, Hedenstierna et al. 1990).

4.6 NDL insufflation of oxygen during OLA, all groups

Oxygen, at a flow rate of 2 $l.min^{-1}$ was insufflated with an 8 French catheter gauge down the lumen of the NDL. The reason for the use of oxygen insufflation was to minimize the incidence of hypoxia during OLA (Capan, Turndorf et al. 1980). Furthermore, reports in the literature express concern regarding hypoxia during administration of dobutamine and other beta-adrenoreceptor stimulants (Voelkel 1986).

Insufflation of oxygen down the NDL lumen of the DLT at an airway pressure of zero was not effective in improving arterial oxygenation during OLA in either Capan et al's or Alfery and colleagues' studies, whereas it was effective in Rees and Wansbrough's study (Rees and Wansbrough 1982a; Alfery, Benumof et al. 1981; Capan, Turndorf et al. 1980). Benumof criticizes the Rees and Wansbrough study because they did not use patients as their own controls as done by Alfery in their dog study (Alfery, Benumof et al. 1981); rather Rees and Wansbrough used a separate control group with which to compare the effects of NDL insufflation on oxygenation (Benumof 1991). Whether this is valid criticism is uncertain. What is not clear is why these conflicting reports appear in the literature on the efficacy of NDL oxygen insufflation. The conflicting reports on the use of oxygen insufflation stand in contrast to the consistent improvement brought about by low levels of NDL CPAP (Hogue 1994). For instance, administration of NDL CPAP at values as low as 2 cm H_2O is reported to benefit arterial oxygenation during OLA in the LDP (Hogue 1994). The differences between CPAP and oxygen insufflation in their efficiency in improving oxygenation may be related to the mechanisms whereby they work. In the absence of ventilation, both of these techniques rely on the mass diffusion of oxygen into the alveoli. This requires a patent airway, denitrogenation, and the presence of high partial pressures of oxygen in the airway (Cohen 2001; Sue and Wasserman 1991). It is suggested that all the aforementioned conditions may not be met by oxygen insufflation (Rees and Wansbrough 1982a). However Rothen and colleagues describe that the pressure needed to expand virtually all atelectatic areas that develop under anesthesia is an inflation to vital capacity accompanied by an airway pressure (transpulmonary pressure) of 40 cm H_2O (Rothen,

Sporre et al. 1993). These observations underscore the questionable effects of insufflated oxygen into the NDL as treatment of hypoxemia during OLA. Nonetheless, a number of authors suggest that the CPAP induced transpulmonary pressure gradient possibly exceeds the critical opening pressure in a large percentage of NDL alveoli (Benumof and Alfery 2000; Hogue 1994; Benumof 1991; Alfery, Benumof et al. 1981). This will maintain a degree of alveolar patency in the "collapsed lung".

The use of the large 14 French gauge catheter in Rees and Wansbrough's study could have partially occluded the Robertshaw DLT lumen and created NDL CPAP. However, these authors specifically state in their methods that the large catheter introduced into the DLT's *did not* occlude the lumen of the DLT in their study. In the current study a smaller 8 French gauge catheter was used for oxygen insufflation. The use of the thin catheter was in order to prevent NDL CPAP from developing as a result of the catheter completely or partially occluding the airway.

Another possible explanation for the difference between Rees and Wansbrough, and Alfery and colleagues' studies is that the former authors started administering oxygen when OLA was first initiated, whereas the latter authors first conducted various manoeuvres and only later started insufflating oxygen down the NDL lumen of the DLT. In the Rees and Wansbrough study, the NDL oxygen insufflation catheter was introduced immediately after two-lung ventilation with 100% oxygen had ceased. The effect of ventilation with 100% oxygen would have meant that two of the criteria mentioned above (the presence of oxygen and denitrogenation) would most likely have been fulfilled in Rees and Wansbrough's study. This would have facilitated movement via mass diffusion of oxygen down the airways to the alveoli. However, it is possible that in the Capan study, by the time oxygen was insufflated down the NDL airway, any oxygen remaining in the airways after the cessation of two-lung ventilation would have been absorbed (Rees and Wansbrough 1982a; Capan, Turndorf et al. 1980). This discussion introduces a hypothesis that would be interesting to test.

It is also important to consider the importance of NDL oxygen insufflation in the light of the very high mixed venous oxygen saturations approaching and frequently exceeding 90% in the current study. Thus, even in the presence of a large shunt, the high mixed venous oxygen tensions ensured that arterial hypoxia was unlikely to occur. Therefore any potential benefit of NDL oxygen insufflation becomes of lesser importance. It is also unclear whether oxygen insufflation benefited the patients in our study because there was no control group in which this technique was not used.

In retrospect, in the light of the inconsistencies in the literature regarding the effectiveness of NDL oxygen insufflation, the use of low levels of NDL CPAP could have been considered instead. The counterarguments to this contention are firstly, similar amounts of CPAP would have differing effects on NDL volume because of different NDL compliances. Secondly, NDL CPAP may have interfered with the surgical field. This would however have introduced another confounding factor in determining the effect of venous oxygenation on arterial oxygenation during OLA. Possibly, oxygen insufflation should have been avoided altogether in the conduct of this study.

4.7 Dobutamine during OLA

The part of the hypothesis relevant to this section is that RV afterload will increase during OLA. Such an increase in

afterload will deleteriously affect RV-PA coupling, and therefore RV performance. Dobutamine is an inotropic agent that has salutary effects on RV afterload. It is therefore considered to be a particularly suitable drug to use in circumstances where RV afterload is increased (Wolfer, Krasna et al. 1994; Coddens, Delooft et al. 1993; Mathru, Dries et al. 1990; Dell'Italia, Starling et al. 1985; Jardin, Gueret et al. 1985; Dell'Italia, Starling et al. 1985). It was therefore hypothesized that inotropic support with dobutamine would favorably readjust RV coupling to its load during OLA.

4.7.1 Dobutamine during OLA: opposition to pulmonary flow

During the administration of dobutamine 5 and 7 ug.kg^{-1}.min^{-1}, mean PA pressure increased by 33% compared to the steps when the patients were awake and when two-lungs were being ventilated. Systolic PA pressure increased by between 23 and 33% during the steps when dobutamine was administered (i.e. OLA plus dobutamine 3, 5 and 7 ug.kg^{-1}.min^{-1}) compared to the steps when dobutamine was not administered (i.e.the steps when patients were awake, when two-lungs were being ventilated and during the OLA step during which dobutamine was not administered) (Table 3.3.2.9). PA elastance increased by 30% during administration of dobutamine 5 ug.kg^{-1}.min^{-1} compared to when the patients were awake (Table 3.3.2.12). PVR increased by up to 39% during administration of dobutamine 5 ug.kg^{-1}.min^{-1} compared to either OLA without dobutamine, or when either dobutamine 3 or 7 ug.kg^{-1}.min^{-1} was administered (Table 3.3.2.12). The PA time constant decreased by 70% during infusion of dobutamine 7 ug.kg^{-1}.min^{-1} compared to the two-lung anesthesia step (Table 3.3.2.13). PA compliance was decreased by up to 61% when dobutamine 5 and 7 ug.kg^{-1}.min^{-1} were infused compared to the OLA step when dobutamine was not administered (Table 3.3.2.13).

While dobutamine was being administered during OLA, mean PAP increased to a maximum of 24.9 ± 6.2 mm Hg at a cardiac index of 5.5 ± 1.2 l.min^{-1}.m^{-2}. However during OLA, in the control group, mean PAP was 24.0 ± 7.7 mm Hg at the maximum cardiac index of 4.4 ± 1.1 l.min^{-1}.m^{-2}. This represents a relatively limited rise in PA pressure on administration of dobutamine compared to the increease in mean PAP observed during OLA alone. Three possible reasons exist as to why there may have been a limited increase in mean PAP while dobutamine was being administered:

1. The “blow off” effect via the NDL vasculature may have limited the rise in PA pressure (See discussion on 3rd last paragraph of section 4.2 for discussion of the “blow-off effect”).
2. The lung tissue could have been less damaged in this than in the other two groups. The implication of the preceding statement is that the pulmonary vascular reserve of patients in this group may have been better preserved so that the increase in cardiac output on administration of dobutamine did not exhaust their pulmonary vascular recruitment and dilation reserve. However, demographic data does not reveal differences between the groups in terms of preoperative pulmonary function. This reason is therefore unlikely to be a valid explanation for this phenomenon.
3. The possibility exists that dobutamine administration induced pulmonary vasodilatation (Lejeune, Naeije et al. 1987; Lejeune, Leeman et al. 1987). This issue will be discussed under the heading of “dobutamine and arterial oxygenation”.

During the infusion of dobutamine 5 ug.kg^{-1}.min^{-1}, PVR exceeded that observed during the OLA, dobutamine 3 and 7 ug.kg^{-1}.min^{-1} steps. However, this increase in PVR does not represent a clinically significant increase in PVR.

Further evidence that this increase in PVR is not significant, is the observation that this "*increase in PVR*" did not differ statistically or clinically from the baseline awake, or two lung anesthesia steps.

PA compliance represents one of the factors determining vascular impedance in the 3-element Windkessel model of the circulation (Fourie, Coetzee et al. 1992; Fourie, Coetzee et al. 1992b). Why then did PA compliance decrease with the administration of dobutamine? To answer this question, the factors deteremining compliance can be studied. In the current study, PA compliance was derived from the quotient of the PA time constant and total pulmonary vascular resistance (Laskey, Parker et al. 1990; Visser 1989). Total pulmonary vascular resistance did not change, whereas the PA time constant decreased by 70% on administration of dobutamine 7 $ug.kg^{-1}.min^{-1}$ compared with one lung anesthesia when dobutamine was not administered. Heart rate also plays a role in determining the PA time constant. In this respect, it must be noted that increases in dobutamine dosage iwere assosiated with progressive increases in heart rate in the current study. Such increases in heart rate are associated with decreases in diastolic time and therefore decreases in the PA time constant (Thys, Dauchot et al. 1999). This decrease in the time constant explains mathematically why the increase in PA compliance occurred.

The conceptual reasons for the decrease in PA compliance can be explained as follows. The implication of the administration of dobutamine was to increase the amount of blood residing in the PA for the following reasons:

1. Firstly, the administration of dobutamine was associated with an unchanged stroke volume; however its administration resulted in an increase in heart rate compared to OLA alone. Therefore, more blood was ejected into the PA per unit time and,
2. Secondly, because of the decrease in diastolic time associated with the increase in heart rate on administration of dobutamine, runoff of blood into the left atrium may not have been complete by the time the next systole occurred.

This greater volume of blood remaining in the PA means that the increase in pressure for a certain stroke volume will be greater than if the PA were emptier and more compliant. In simple words, the PA is stiffer, like a car tyre that has been inflated from a floppy structure to one with stiff walls. This "inflation" is observed as a decrease in PA compliance.

Other factors that could possibly have played a role in the decrease in PA compliance include:

- The effect of a decreased runoff time will be further aggravated by a higher PVR,
- Sympathetic nervous system stimulation has been shown to decrease pulmonary vascular compliance (Hennebry and Gerstenblith 2001) and,
- A stiffer PA with lower compliance will increase elastic recoil. This increase in PA elastic recoil will cause the diastolic pressure decline in the pulmonary artery to be more rapid. In other words, the PA will tend to empty in a shorter time. This is reflected by a decrease in the time constant of the PA diastolic delay curve.

4.7.2 Dobutamine during OLA: RV performance

All dosages of dobutamine administered during OLA increased cardiac output compared to OLA when dobutamine was not administered, and the baseline awake state and when two lungs were being ventilated (Table 3.3.2.10). However, no progressive increase in cardiac output was seen as the dose of dobutamine was increased (Table 3.3.2.10). The only change in stroke volume in this group was observed during administration of dobutamine 3

ug.kg^{-1}.min^{-1}, when stroke volume was greater than that measured during two lung anesthesia (Table 3.3.2.10). Further increases in the dobutamine dose were not assosiated with increases in stroke volume (Table 3.3.2.10). Nonetheless, dobutamine infusions did raise cardiac output by increasing heart rate (Table 3.3.2.10). RVSWI increased during administration of dobutamine 3 and 7 ug.kg^{-1}.min^{-1} compared to the baseline awake and two-lung anesthesia steps (Table 3.3.2.15). However, administration of dobutamine did not improve RVEF or decrease RVEDVI or CVP (Tables 3.3.2.10, 3.3.2.3.3.2.11 and 3.3.2.15).

The lack of increase in stroke volume at higher dosages of dobutamine necessitates comment. Reasons include:

- It is likely that the increases in opposition to pulmonary flow observed to occur concomitantly with the infusion of dobutamine, (predominantly an increase in PA elastance and a decrease in PA compliance), deleteriously affected RV performance.
- Both Piene and Sundt, and Fourie and Coetzee and colleagues have studied the effect of PA compliance on coupling of the RV to the pulmonary vasculature (Fourie, Coetzee et al. 1992b; Piene and Sund 1979). Piene and Sundt suggested that the normal (high) PA compliance enhances power transmission between the RV and the pulmonary vasculature (Piene and Sund 1979). If impedance is low and PA compliance high, less energy is wasted on pulsatile flow in the pulmonary vasculature (Hennebry and Gerstenblith 2001). Under circumstances of low impedance and high compliance, the blood flow in the PA takes on a more continuous pattern. Fourie and Coetzee and colleagues demonstrated that decreases in compliance impair the delivery of RV stroke volume (Fourie, Coetzee et al. 1992b; Piene and Sund 1979). This is because a decrease in PA compliance will increase peak pressures and amplify the oscillatory nature of the movement of blood through the lungs. The increased energy expended does not benefit forward flow and is therefore wasted energy (Hennebry and Gerstenblith 2001).
- As animal ventricles are paced at faster and faster rates, stroke volume has been observed to decrease progressively (West 1989). The explanation given for this observation is that increases in heart rate decreases diastolic filling time that limits further increases in stroke volume. In the current study, as higher dosages of dobutamine were administered, heart rate increased progressively. This decrease in filling time may have contributed to the lack of increase in stroke volume as the dose of inotrope was increased.
- The effect of ventricular interdependence on RV function can be speculated on. Opposition to RV ejection increased with the administration of dobutamine. However, systemic pressures did not increase above baseline. It could be speculated that if systemic pressures had increased because of the administration of an inotrope, greater transseptal transmission of force (pressure) from the left to the right ventricle could have occurred. This may have assisted RV function in the face of an increase in opposition to RV ejection.
- It must be noted that an increase in heart rate to near the usual impedance minimum at 2 hertz (Hennebry and Gerstenblith 2001) accompanied the administration of dobutamine. As the impedance spectrum *per se* was not measured in this study, it is difficult to comment as to whether this increase in heart rate had either a beneficial or deleterious effect on RV performance.

In summary, regarding the effects of dobutamine infusions on opposition to pulmonary flow and RV performance during OLA:

1. Low rates of dobutamine infusion (3 ug.kg^{-1}.min^{-1}) increase in cardiac output, stroke volume, and RVSWI.

The administration of dobutamine 3 ug.kg^{-1}.min^{-1} was not accompanied by increases in RV afterload. Therefore, low infusion rates of dobutamine did benefit RV-PA coupling during OLA as evidenced by increases in cardiac output, stroke volume, and RVSWI.

2. However, administration of higher dosages of dobutamine (5 and 7 ug.kg^{-1}.min^{-1}) during OLA increased the opposition to pulmonary blood flow. There were increases in mean PAP and PVR: both these increases are considered to have limited clinical significance. However, the decrease in PA compliance during the infusion of the highest dosage of dobutamine appears to be clinically significant. The increases in opposition to pulmonary flow and lack of progressive increase in indices of RV performance are in contrast to what is expected to occur on administration of the inotrope and pulmonary vasodilator, dobutamine. It is likely that the pulmonary vascular reserve during OLA was exhausted at the high cardiac indices of 5 to 5.5 l.min^{-1}.m^{-2} and this overshadowed the expected pulmonary vasodilator effects of dobutamine. Moreover, it is probable that the increase in RV afterload was significant enough to prevent its performance increasing as would be expected with the administration of progressively higher dosages of inotrope (Domino 1997).

The hypothesis relevant to section 4.7 was that the combined inotropic and pulmonary vasodilatory properties of dobutamine would improve impaired RV performance during OLA. Low dosages of dobutamine administration did, whereas higher dosages did not, improve the coupling between the RV and its afterload during OLA. The hypothesis for this section can therefore not be accepted without qualification.

4.8 Dobutamine during OLA: oxygenation

The relevant part of the hypothesis for this section was that the impairment of RV performance secondary to the increase in RV afterload imposed by OLA would be improved by administration of dobutamine. Inotropic support will restore oxygen delivery to normal. The increase in the DO_2/VO_2 ratio will improve P□O_2, and in the presence of the large shunt present during OLA, improve arterial oxygenation (Kelman, Nunn et al. 1967).

The patients in the present study did not become hypoxic during OLA when the cardiac output increased concomitantly with the administration of dobutamine (Russell and James 2000; Lejeune, Naeije et al. 1987; Lejeune, Leeman et al. 1987; Bishop and Cheney 1983; Marin, Orchard et al. 1979). However, dobutamine administration did not decrease PaO_2 or arterial oxygen saturation (Tables 3.3.2.5), and neither did it increase the cost of oxygenation (i.e. shunt fraction, alveolar-arterial oxygen partial pressure gradient, or PaO_2/FiO_2 ratio (Tables 3.3.2.7)) during OLA compared to when OLA was conducted without dobutamine administration. These observations differ from other studies demonstrating hypoxemia when vasodilatory amines are administered during both two (Lejeune, Naeije et al. 1987; Lejeune, Leeman et al. 1987; Bishop and Cheney 1983; Marin, Orchard et al. 1979) and one lung ventilation (Russell and James 2000). Theoretically, the influence of dobutamine on arterial oxygenation during OLA may be related to the balance of the following divergent effects (Mathru, Dries et al. 1990; Lejeune, Naeije et al. 1987; Lejeune, Leeman et al. 1987; Marin, Orchard et al. 1979):

1. By improving the relationship between oxygen delivery and consumption, dobutamine increases P□O_2. This increase will benefit arterial oxygenation in the presence of a large shunt,
2. The above has to be weighed against possible increases in VO_2 induced by dobutamine, the consequence

of which will be a decrease in P□O_2 (Karzai, Lotte et al. 1996; Karzai, Gunnicker et al. 1996; Karzai, Gunnicker et al. 1994),

3. Increased PA pressure accompanying the increased cardiac output will inhibit HPV and increase shunt (Benumof 1985; Benumof and Wahrenbrock 1975),
4. Direct inhibition of HPV by dobutamine (Lejeune, Naeije et al. 1987; Marin, Orchard et al. 1979) and,
5. The influence of P□O_2 on HPV (i.e. high levels of venous oxygenation will inhibit and low levels will potentiate HPV) (Benumof 1985; Domino, Wetstein et al. 1983; Marshall and Marshall 1983; Benumof, Pirlo et al. 1981).

As discussed already, Kelman and co-workers were the first to report on the theoretical influence of mixed venous oxygenation on arterial oxygenation during anesthesia (Kelman, Nunn et al. 1967). During OLA, only two studies, one in humans (Mathru, Dries et al. 1990) and the other in an animal model (Russell and James 2000) have directly attempted to address arterial oxygenation by administering inotropes to increase oxygen delivery. These studies have produced inconsistent results (Mathru, Dries et al. 1990). Mathru and colleagues administered 5 $ug.kg^{-1}.min^{-1}$ of dobutamine to patients undergoing pneumonectomy during OLA in the LDP (Mathru, Dries et al. 1990). The details of their methodology deserve comment when considering their results or on making comparisons with the present study. Many aspects of the basic study design are comparable to those of the current study:

1. Premedication, non-depolarising muscle-relaxant usage, monitoring techniques, methods of measuring oxygenation and both the type and determination of the position of the DLT were similar in the Mathru and the current studies. Furthermore, ventilation was titrated so that peak airway pressures were limited to 20 cm H_20 (which were lower than in the current study) (Table 3.3.2.2) and no DL PEEP was applied. However, ventilation was titrated to an unspecified value of "normocapnia". This ventilatory technique resulted in $PaCO_2$ values of 5.2 ± 0.7 and 5.3 ± 0.5 kPa in the control and dobutamine steps respectively. As in the current study, their patients were also ventilated with 100% oxygen. Mathru et al. state they maintained normovolemia, although details of how this was achieved were not specified.
2. The patients had carcinoma of the "lung." Mathru and colleagues state that preoperative pulmonary function was within normal limits. This is different from the majority of the lung function test results obtained in the current study.
3. As in the current study, they also compared hemodynamics, venous and arterial oxygenation with and without the administration of dobutamine. Furthermore, their observations were obtained 15 minutes after thoracotomy and OLA had commenced. A similar time period and sequence of events was used in the current study.
4. Albeit only one dose of dobutamine was used, this was infused at the same rate as one of the dosages used in the current study.

Certain differences in study design and results are apparent. Oxygen was not insufflated down the NDL lumen of the DLT in the Mathru study. Mathru and colleagues used enflurane alone to provide anesthesia. They did not specify the partial pressure used. Furthermore, cardiac output was only 2.37 ± 0.2 $l.min^{-1}.m^{-2}$ during OLA. This appears to be lower than the cardiac output in the current study under OLA. This is possibly the result of depression by the unspecified concentration of enflurane. Additionally, oxygen consumption in their patients was higher than in the

current study (see table 4.8.1). They do not report body temperature, neither do they normalize VO_2 for body weight and body surface area, nor do they give the relevant demographic data. This means that that the patients in the current and Mathru studies cannot be compared. However, if it is assumed that normal BSA is approximately 1.73 m^2, the oxygen consumption in their patients was 158.3 ± 38.0 and 164.5 ± 15.9 $ml.min^{-1}.m^{-2}$ respectively during OLA at baseline and when dobutamine 5 $ug.kg^{-1}.min^{-1}$ was being administered. Therefore, if the current and the Mathru studies are compared, it is likely that the balance between a greater oxygen demand and a diminished supply during OLA in the Mathru study resulted in an S□O_2 of only 60% during baseline OLA. In the current study, mixed venous saturations during baseline OLA in the dobutamine group were 90.6 ± 4.7 kPa. It is probably reasonable to conclude that, compared with the current study, systemic oxygenation in Mathru and co-workers' patients started from a lower baseline (i.e. a lower ratio of oxygen delivery to consumption) before the administration of dobutamine commenced.

On administration of dobutamine during OLA in Mathru and colleagues' study, cardiac output and oxygen delivery increased by 23% and 35% respectively compared with baseline, whereas no increase in oxygen consumption was seen. The result was a 24% increase in S□O_2 to 74.6 ± 2.8 %. Concomitantly, PaO_2 increased from 10 ± 1.8 kPa to 33.3 ± 6 kPa. In other words, the administration of dobutamine normalized the mixed venous oxygen tension and thereby significantly improved arterial oxygenation. In spite of the administration of dobutamine and the increase in cardiac output, the shunt fraction *decreased* from 33.2 ± 6.2 to 20.2 ± 2.9 %. It is noteworthy that mean PAP actually decreased when they administered dobutamine (Table 4.8.1). It implies that their patients, who had normal preoperative lung function tests, had adequate pulmonary vascular reserve at the flows generated. Furthermore, in spite of the increase in cardiac output, the decreased PA pressure would have had minimal deleterious influences on HPV and shunt during OLA. Therefore, in contrast to the current study, Mathru and colleagues were successful in employing the increased delivery and unchanged consumption of oxygen to improve (normalise) mixed venous oxygenation and thereby arterial oxygenation during OLA.

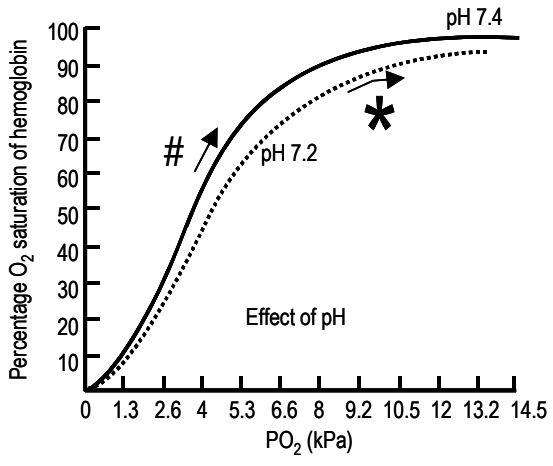

Figure 4.8.1 *ODC's for patients with normal and lower pHs. The initial position of mixed venous oxygenation in the current and Mathru study are indicated. The benefit of increasing cardiac output for Mathru's normocarbic# and the current study's hypercarbic* patients is shown.*

Redrawn from Chapter 35 "Gas transport between the lungs and the tissues" in WF Ganong. Review of medical physiology, 19th edition. Appelton & Lange, Stamford, Connecticut, 1999.

	OLA		OLA and Dobutamine		p
	□	SD.	□	SD.	
Heart rate (beats.min^{-1})	73.8	8.1	80.0	7.1	$p < 0.01$
Stroke index (ml.m^{-2})	32.4	4.1	36.6	5.0	$p < 0.01$
Cardiac index (litres.min^{-1}.m^{-2})	2.4	0.2	2.9	0.5	$p < 0.01$
LVSWI (g.m.m^{-2})	34.9	5.4	41.8	6.7	$p < 0.01$
RVSWI (g.m.m^{-2})	8.6	1.8	8.2	1.8	Not significant
MAP (mm Hg)	89.9	5.9	93.6	4.3	$p < 0.01$
PAP (mean) (mm Hg)	18.7	3.3	17.4	2.5	$p < 0.05$
PAWP (mm Hg)	11.1	1.4	10.4	1.6	Not significant
PVR (mm Hg.litres^{-1}.min^{-1})	1.7	0.7	1.3	0.5	$p < 0.01$
PaO_2 (kPa)	9.97	1.8	33.5	5.9	$p < 0.01$
S□O_2 (%)	60.0	8.9	74.6	2.8	$p < 0.01$
Shunt fraction (%)	33.2	6.3	20.2	2.9	$p < 0.01$
CaO_2 (ml.100 ml^{-1})	16.0	0.9	17.7	1.1	$p < 0.01$
C□O_2 (ml.100 ml^{-1})	10.2	1.6	12.7	0.8	$p < 0.01$
CcO_2 (ml.100 ml^{-1})	18.9	1.0	18.9	1.0	Not significant
Oxygen delivery (ml.min^{-1})	755.4	66.4	1021.8	106.1	$p < 0.01$
VO_2 (ml.min^{-1})	273.9	65.8	284.5	27.5	Not significant

Table 4.8.1 Data from Mathru's study (Mathru, Dries et al. 1990). Anesthesia was maintained with enflurane (partial pressure not reported) in 100% oxygen. Dobutamine 5 ug.kg^{-1}.min^{-1} was administered during OLA with favourable effects on cardiac output, mixed venous and arterial oxygenation. Oxygen consumption did not change during administration of dobutamine. Note the low starting mixed venous oxygen saturation and its improvement with the administration of dobutamine. 7 subjects were included in the study and Student's-t test was used to compare the groups.

The decrease in shunt in Mathru's and colleagues study is interesting. The Mathru paper find it "*difficult to explain*" the decrease in shunt fraction. The shunt equation, Qs/Qt = (CcO_2 – CaO_2)/(CcO_2 – $C\square O_2$), considers the ratio of the difference between pulmonary capillary and arterial oxygen content to the difference between pulmonary capillary and mixed venous blood. In the Mathru study, because of the steep part of the oxygen dissociation curve on which they are operating, the increase in cardiac output raised venous saturation and content by 2½ times as much as the rise in arterial content. However, because of the shape of the ODC, the increase in arterial oxygen tension had a much smaller effect on SaO_2 and CaO_2. CcO_2 would not be affected by the administration of dobutamine. Therefore the different starting positions on the ODC of these parameters and how they were influenced by the greater increase in oxygen delivery relative to VO_2, explains this phenomenon of "a decrease in shunt fraction".

	OLA		OLA and Dobutamine		p
	□	SD.	□	SD.	
Heart rate (beats.min^{-1})	99.0	8.0	109.0	12.0	$p < 0.05$
MAP (mm Hg)	87.0	15.0	95.0	9.0	Not significant
Cardiac index (litres.min^{-1}.m^{-2})	3.3	0.3	4.1	0.4	$p < 0.05$
PAP (mean) (mm Hg)	18.0	3.0	21.0	3.0	$p < 0.05$
PAWP (mm Hg)	9.1	2.4	10.0	2.5	Not significant
PVRI (dynes.s.cm^{-5}.m^{-2})	215	68	212	55	Not significant
Qs/Qt (%)	29.2	7.0	26.0	6.2	$p < 0.05$
pH	7.39	0.03	7.38	0.04	Not significant
$PaCO_2$ (kPa)	4.9	0.4	5.0	0.4	Not significant
PaO_2 (kPa)	22.3	6.1	26.6	6.9	$p < 0.01$

Table 4.8.2 Data adapted from (Nomoto and Kawamura 1989). Dobutamine 5 ug.kg^{-1}.min^{-1} was administered during OLA with favourable effects on cardiac output and arterial oxygenation. Venous oxygenation data is not reported in their study. Inspired oxygen fraction was varied between 0.5 to 1.0 in this study. 7 subjects were included in the study and Student's-t test was used to compare the groups.

Thus, from consideration of Mathru's work, it appears that not only is the ratio of VO_2 to DO_2 important in determining $P\square O_2$, but the initial position of the ODC also plays an important role. Thus, if the $P\square O_2$ starts from a low position on the steep part of the ODC and then increases because the DO_2/VO_2 ratio improves because of administration of dobutamine, significant benefits on venous oxygenation will be seen. Furthermore, whereas Mathru's patients were

normocarbic, the patients in our study were hypercarbic. The ODC is shifted to the right by hypercarbia (West 1985). This rightward shift of the ODC in the current study would have ensured that the working position of the very high venous saturations would have been on the flat part of the curve. Therefore, in the current study, increasing the DO_2/VO_2 ratio did not benefit arterial oxygenation because of the starting position of P□O_2 on the ODC. Furthermore, the initial position on the ODC of C□O_2 plays a role in determining the effect of an increase in cardiac output on the calculation of the "virtual" shunt.

The differences and similarities between Mathru and colleagues' and the current study also highlight other important points. As mentioned, with respect to cellular oxygenation, the patients in the Mathru study started from a low baseline position on the steep part of the ODC and improved with dobutamine administration. However, administration of the inotrope did not improve the already high P□O_2 in the current study. The difference between these studies lies not only in the higher cardiac index and presumably higher oxygen delivery of the current study, but also the lower oxygen consumption seen during OLA in the present study. It is likely that the anesthetic techniques used in these two studies were responsible for the different cardiac indices observed. The decrease in VO_2 in the current study is most likely the result of the anesthetic technique used; the small decrease in temperature on induction would also have contributed to this phenomenon.

	OLA		OLA and Nitroglycerine		p
	□	SD.	□	SD.	
Cardiac index (litres.min^{-1}.m^{-2})	3.4	0.6	2.9	0.7	$p < 0.05$
PAP (mean) (mm Hg)	19.0	4.0	17.0	3.0	$p < 0.05$
PAWP (mm Hg)	10.0	2.7	9.8	2.8	Not significant
Qs/Qt (%)	29.2	4.9	34.6	5.0	$p < 0.01$
PaO_2 (kPa)	24.6	4.0	19.1	3.8	$p < 0.01$

Table 4.8.3 Data adapted from (Nomoto and Kawamura 1989). Nitroglycerine 1 ug.kg^{-1}.min^{-1} was administered during OLA with deleterious effects on cardiac output and arterial oxygenation. Inspired oxygen fraction was varied between 0.5 to 1.0 in this study. 7 subjects were included in the study and Student's-t test was used to compare the groups.

To illustrate the effects of the increase in oxygen delivery and decrease of VO_2 on arterial oxygenation, values representative of oxygen consumption and cardiac index typically seen during OLA in the current and Mathru and colleagues' studies were entered into the modified Fick formula described by Kelman and colleagues (Equation 4.4.2.4). The discrepancy between the Mathru and the current studies is apparent in the graphs that result (Figure 4.4.2.3). The cardiac outputs of the patients in the current study place them on the flat portion of the relationship

between CaO_2 and cardiac index where further increases in flow do not provide better arterial oxygenation. A patient in Mathru's study with a starting cardiac index of 2.37 $l.min^{-1}.m^{-2}$, would experience an improvement in arterial oxygen content when cardiac output increased from 2.4 ± 0.2 to 2.91 ± 0.5 kPa at an unchanged VO_2 of 164 $ml.min^{-1}.m^{-2}$.

A limitation of the use of the Kelman curves is that other effects such as the influence of PA pressure and dobutamine on the shunt and the changing $P\square O_2$ as VO_2 increases with inotrope administration during OLA, are not taken into account in these graphs. However, graphic relationships between cardiac index and arterial oxygen content are still useful tools with which to understand both Mathru's and the current study, as in neither study was oxygen consumption affected by the administration of dobutamine.

Nomoto and Kawamura investigated the effects of dobutamine and nitroglycerine on oxygenation during OLA (Nomoto and Kawamura 1989). Inspection of their results reveals that their patients had close to normal preoperative lung function tests. Anesthesia was maintained with enflurane (partial pressures also unspecified) and nitrous oxide. Pancuronium was administered as the non-depolarising muscle-relaxant. Lung separation was achieved by using a Robertshaw DLT. A tidal volume of 12 $ml.kg^{-1}$ was delivered at a respiratory rate of 12 breaths per minute during OLA. The resultant $PaCO_2$ was 5.0 ± 0.04 kPa. On the one hand, the administration of nitroglycerine during OLA decreased both cardiac index and arterial oxygenation (Tables 4.8.2 and 4.8.3). On the other hand, dobutamine 5 $ug.kg^{-1}.min^{-1}$ improved cardiac index, but only to values that were similar to those observed in our patients during OLA before inotrope was administered. This improvement in cardiac index was associated with an increase in arterial oxygenation and a decrease in shunt fraction during OLA. These changes in arterial oxygenation could have occurred as a result of changes in mixed venous oxygenation that accompanied the opposing effects of these two drugs on cardiac output. The aforementioned statement is based on the assumption that, in Nomoto and Kawamura's study, as in the current and the Mathru study, the ratio of oxygen delivery to oxygen consumption increased with increases in cardiac output, and vice versa. It is unfortunate that Nomoto and Kawamura did not report mixed venous oxygenation or oxygen consumption values in their paper so that we could test the validity of these suppositions. However, additional support for the contention that improvement in arterial oxygenation was induced by increases in cardiac index and $P\square O_2$ comes from similar directional changes in shunt fraction as seen in the Mathru study. This observation again supports the assumption made above that mixed venous oxygen tension and cardiac index changes occurred in similar directions in this study. In this respect,

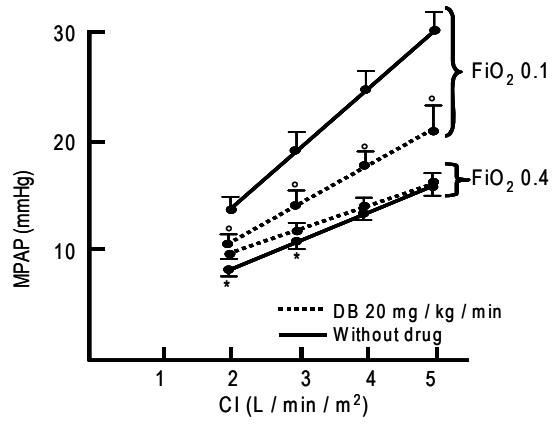

Figure 4.8.2 The pressure vs. flow plots while dobutamine was administered to 8 dogs experiencing alveolar hypoxia (F_iO_2 0.125) or while a F_iO_2 of 0.4 was administered. Dobutamine did not decrease PVR in the hyperoxic group unlike the decrease in PVR seen in the hypoxic group. Data represented as mean and SEM. The groups differ significantly $p < 0.05$. The graph has been redrawn from Lejeune et al, 1987.

it is noteworthy that the administration of dopamine failed to improve cardiac index and arterial oxygenation in this study. This absence of change again supports the hypothesis that the main reason for the improvement or worsening of arterial oxygenation seen by Nomoto and Kawamura was the influence of cardiac output on the DO_2/VO_2 ratio. As in Mathru's study, Nomoto and Kawamura's patients had normal lung function tests and probably had normal pulmonary vascular reserve. The subsequent lack of increase in mean PAP and PVRI during administration of dobutamine also implies that these factors did not influence HPV during OLA. This emphasises that increases in P□O_2 were mainly responsible for the improvements in PaO_2 seen with dobutamine.

	Enflurane		Isoflurane		Differences, if any, between the two groups
	□	SD.	□	SD.	
Cardiac index (litres. $min^{-1}.m^{-2}$)	2.7	1.0	3.0	0.9	Not significant
PaO_2 (kPa)	16.4	6.0	21.2	7.0	p = 0.002
P□O_2 (kPa)	6.2	1.0	6.8	1.0	p = 0.003
Qs/Qt (%)	41.0	3.0	39.0	4.0	Not significant
Oxygen consumption ($ml.min^{-1}.m^{-2}$)	71.9	11.0	75.8	14.0	Not significant

Table 4.8.4 Adapted from Slinger and Scott 1995. Data obtained after 30 minutes of OLA during which period an end tidal partial pressure of 1 MAC of either anesthetic had been administered. 7 subjects were included in the study and Student's-t test was used to compare the groups.

Previous studies have shown that at similar MAC values, isoflurane produces a better PaO_2 during OLA than halothane (Benumof, Augustine et al. 1987). Slinger and Scott compared the effect of equipotent dosages of isoflurane and enflurane on PaO_2 during OLA in the LDP. They were also interested in investigating whether the different hemodynamic effects of these agents influenced arterial oxygenation during OLA (Slinger and Scott 1995). After induction of anesthesia, patients were administered 1 MAC of either isoflurane or enflurane. Muscle relaxation was attained using pancuronium. Tidal volumes of 10 $ml.kg^{-1}$ were administered during OLA and the respiratory rate was adjusted to keep the $PaCO_2$ between 4.6 to 6.0 kPa. Their results demonstrated a linear relationship between cardiac output and PaO_2 (Figure 4.8.3). Furthermore, isoflurane anesthesia resulted in a higher PaO_2 than enflurane during OLA. However, there were only a small number of patients in whom pulmonary artery catheterisation could be justified on clinical grounds. There was no statistically significant difference between the cardiac outputs generated when anesthesia was conducted with either of these two anesthetic agents. Thus, in that study, they demonstrated that PaO_2 could be improved by increasing cardiac output. Nonetheless, they failed to demonstrate that an anesthetic technique related improvement in cardiac output actually resulted in better arterial oxygenation (Pagel, Farber et al. 2000; Eger 1994).

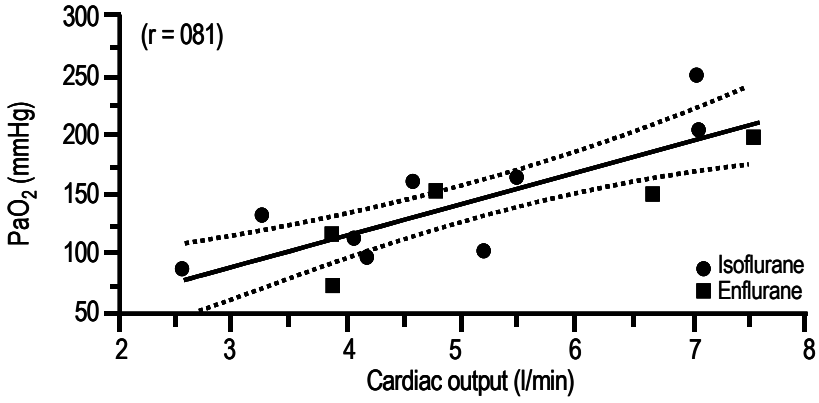

Figure 4.8.3 The relationship of arterial oxygenation and cardiac output during OLA with either isoflurane or enflurane. A significant relationship exists between PaO_2 and cardiac output ($p < 0.001$, $r = 0.81$, $n = 7$). Redrawn from Slinger and Scott, 1995.

From the data presented in Slinger and Scott's paper, their patients mean body surface area can be calculated to be 1.78 m^2. This enables comparisons to be made with other studies (Table 4.8.4). Shunt, VO_2 and cardiac output did not differ between the groups. However, the difference in P□O_2 between the groups suggests that these normocarbic patients were located on the steep part of the ODC. However, hemoglobin concentrations (and temperatures) were not published in the study. This prevents the calculation of CaO_2 and the location of these patients on the correct part of the Kelman curve. However, the strong relationship between cardiac output and PaO_2 in Slinger and Scott's study raises suspicion that at the cardiac indices at which these patients were operating, they were on a relatively steep part of ODC. Administering inotrope to these patients would have probably improved oxygenation further.

Russell and James also administered inotropes in an attempt to improve cardiac output and mixed venous oxygenation and thereby arterial oxygenation (Russell and James 2000). The subjects of their study were healthy pigs. Anesthesia was maintained with an inspired partial pressure of 1% halothane, while an F_iO_2 of 1 was administered. Ventilation was aimed at maintaining a $PaCO_2$ of between 4 to 6 kPa. Forced air warming was used to keep nasopharyngeal temperatures between 35.5 to 37.5 °C. The temperatures of individual pigs were not reported. The sequence of events in the study was as follows. Firstly, baseline hemodynamics and oxygenation were measured. Thereafter, either an adrenaline or an isoprenaline infusion was administered with the stated aim of increasing cardiac output by at least 30%. Hemodynamics and oxygenation were again measured once the goal had been achieved. The catecholamine infusion was terminated. The pig was then allowed to *"settle usually to within ± 10% of baseline values."* 15 minutes thereafter, "*the second infusion (*the other catecholamine) *was then commenced to achieve the same target increase in cardiac output."*

The inotropes resulted in an increase in cardiac output. This increase varied from 54 to 87% with adrenaline and from 31 to 110% with isoprenaline compared to baseline. The factors affecting oxygenation reported in their paper are summarized in Tables 4.8.5 and 4.8.6.

	Units	Baseline Mean ± SD.	Adrenaline Mean ± SD.	% Change Mean ± SD.	p
Cardiac Output	$l.min^{-1}$	1.3 to 4.3 (SD. not reported)	Not reported	54 to 87% increase	Not reported
C□O_2	$ml.100ml^{-1}$	Not reported	Increased by 1.66 ± 1.03	Not reported	0.003
SaO_2	%	86.9 ± 7.9	82.5 ± 10.6	4.4 ± 3.5	<0.001
Shunt	%	48.1 ± 6.9	64.9 ± 7.8	16.8 ± 5.9	< 0.0001
VO_2	$ml.min^{-1}$	126.2 ± 30.2	133.8 ± 43.7	7.7 ± 25.6	0.42

Table 4.8.5 Information obtained from Russell and James's study (adrenaline administration) presented in tabular form. Significant p values indicate a change from baseline.

	Units	Baseline Mean ± SD.	Isoprenaline Mean ± SD	% Change Mean ± SD.	p
Cardiac Output	$l.min^{-1}$	Not reported	31 to 110 %	Not reported	Not reported
C□O_2	$ml.100ml^{-1}$	Not reported	Increased by 0.64 ± 0.43	Not reported	0.004
SaO_2	%	89.5	84.7 ± 7.7	4.8 ± 3.6	0.0071
Shunt	%	44.9 ± 7.4	59.3 ± 3.7	14.3 ± 4.7	< 0.0001
VO_2	$ml.min^{-1}$	120.5 ± 15.9	137.0 ± 26.6	16.6 v 18.4	0.038

Table 4.8.6 Information obtained from Russell and James's study (isoprenaline administration) presented in tabular form. Significant p values indicate a change from baseline.

Certain questions can be raised concerning this study:

- The final dose of inotrope administered was not reported. Furthermore, the endpoint of titration of the inotrope, the cardiac index, was not increased in a uniform manner. The disparate endpoints of both catecholamine infusion and cardiac output make it questionable whether comparisons can be made between the groups.
- It would be useful to know if these large increase in cardiac output increased PA pressure and thereby increased shunt fraction.
- The conduct of the study was such that after the administration of one drug had been completed, and once hemodynamics had returned to approximately 10% of baseline values, the alternative drug was

administered. Using this sequence of events, it would be expected that measurements would not differ between control epochs. However, Russell and James report a progressive increase in oxygen consumption during successive control periods. In the light of this unstable baseline, it is unclear whether the administration of isoprenaline was the only reason for the increase in VO_2. This problem could have been addressed if there had been a control group.

- The temperature of the animals is not recorded at each step. What is reported is that temperature ranged between 35.5 and 37.5^{o} C. Could the increase in VO_2 have been because of a progressive increase in body temperature induced by the forced air-warming blanket in a subject without an open body cavity?
- The study concludes that the decrease in oxygen saturation and increase in shunt on inotrope administration is attributed to "*the effects of sympathomimetic stimulation on intrapulmonary shunting and oxygen consumption.*" On closer inspection of their data, the increase in VO_2 associated with the administration of the inotrope does not appear to be the cause of the arterial desaturation. If the increase in VO_2 was responsible for an increase in arterial saturation, a decrease in venous oxygenation would have been expected. However, the C□O_2 did not decrease as would be expected if their conclusions were correct, but actually increased by 1.66 ± 1.03 ml.100ml^{-1}. This rise in venous oxygenation is not unexpected as the increase in VO_2 (Figure 4.8.4) was minimal compared with the 54 to 87% increase in cardiac output. Therefore, it was not the catecholamine induced increase in VO_2 that played a role in the worsening hypoxia seen in these pigs. It is more likely that the deleterious effects of catecholamines on intrapulmonary shunting played the dominant role in the worsening hypoxia. It would have been useful to report the baseline venous saturations in this study. Significant differences exist between one the one hand, the Mathru, Nomoto and Kawamura, Slinger and Scott and current studies, and on the other hand, the Russell and James study. These pigs had normal lungs and were not in the LDP. Arterial oxygenation is worse in the supine position during OLA as the beneficial effects of gravity in limiting blood flow to the NDL and limiting shunt are not operative (Pinsky, Desmet et al. 1992). Furthermore, the experimental design resulted in a larger starting shunt fraction during OLA than is commonly seen during OLA in the LDP.

Thus, it is doubtful whether the Russell and James and the human studies are comparable. It does not help solve the question whether increasing arterial oxygenation in humans in the LDP subjected to OLA will be achieved by administering inotropes that increase cardiac output. What this study does say is that catecholamine administration increases shunt and worsens arterial hypoxemia in subjects with normal lungs in the supine position during OLA.

The Russell and James study emphasises one of the great concerns regarding the administration of inotropes during OLA, this being that the administration of inotropes to increase in cardiac output may increase shunt fraction and decrease arterial oxygenation during OLA. Nonetheless, in the current study, dobutamine administration was not associated with a statistically significant increase shunt fraction during OLA. There are two possible broad mechanisms why dobutamine could cause pulmonary vasodilatation and hypoxemia during OLA.

1. Firstly it may be due to direct vasodilatation caused by the drug.
2. Secondly, pulmonary vasodilatation can be secondary to the effects of dobutamine on the circulation. In other words, the effects on PAP, mixed venous oxygenation and possibly pulmonary blood flow may cause

inhibition of HPV and thereby and increases in the shunt fraction.

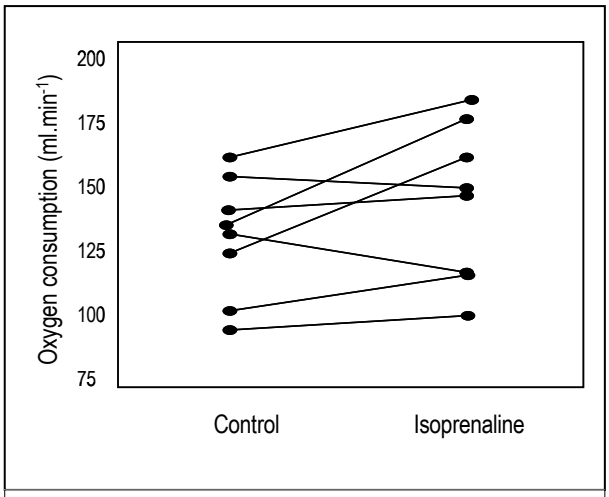

Figure 4.8.4 The increase in oxygen consumption during OLA in pigs administered isoprenaline. "Overall, there was an increase in oxygen consumption (mean 16.6 ± 18.4 ml.min^{-1}, p = 0.038)". Redrawn from Russell and James, 1999

It is not apparent which of the above mechanisms could be responsible for an increase in shunt during OLA. Albeit dobutamine has been suggested to inhibit HPV, this is an inconsistent finding (Capan, Turndorf et al. 1990). Lejeune and colleagues published two studies investigating the aforementioned interaction of dobutamine on HPV (Lejeune, Naeije et al. 1987; Lejeune, Leeman et al. 1987). In their one study, they determined PVR while cardiac output was varied independently of the dosage of inotrope infused. Thus, while a certain dobutamine dosage was infused, a plot of mean PAP versus cardiac index was constructed by varying cardiac output utilizing inferior vena cava occlusion or the opening of an arteriovenous fistula. The mean PAP versus flow plot is considered a more reliable method of determining PVR than one-point determinations thereof (Lejeune, Naeije et al. 1987). Their conclusions indicate that dobutamine does not inhibit HPV at dosages below 10 ug.kg^{-1}.min^{-1}, but does do so at levels greater than this (Capan, Turndorf et al. 1990; Lejeune, Naeije et al. 1987). In their other study on this topic, they discriminate between the effects of dobutamine in "hypoxic" (F_iO_2 0.125) and "hyperoxic" (F_iO_2 0.4) lungs. When the alveolar oxygen tension was low (as it was in the NDL in the current study), Lejeune and colleagues describe that dobutamine induces a progressive dose dependent decrease in pulmonary vascular resistance. However, no pulmonary vasodilatation was observed when the F_iO_2 was 0.4 (hyperoxic lungs) (Figure 4.8.2) (Lejeune, Leeman et al. 1987). An increase in PA pressure would have diverted more blood to the NDL. This could have increased shunt fraction and decreased arterial oxygenation (Pagel and Warltier 1997; Slinger and Scott 1995; Benumof 1991; Capan, Turndorf et al. 1990). Mean PAP rose to its highest level (24.9 ± 6.2 mm Hg) when dobutamine 7 ug.kg^{-1}.min^{-1} was administered but shunt fraction did not rise during OLA during this step.

It must be noted that in the current study, even if the administration of dobutamine had resulted in an increase in shunt fraction, the very high levels of venous oxygenation would have ensured that arterial oxygenation would not have been deleteriously affected. However, the studies by Mathru and colleagues, Nomoto and Kawamura and the current study demonstrate that under usual clinical conditions and low-nornal levels of venous oxygenation during OLA in the LDP, the administration of low dosages of dobutamine do not increase shunt fraction. In fact, the beneficial effect of the increase in cardiac output on venous oxygenation uniformly resulted in a benefit in arterial oxygenation in the study by Mathru and colleagues, and probably in the Nomoto and Kawamura study. Although pulmonary vasodilatation caused by dobutamine remains an area of concern, there is no evidence that its administration worsens arterial oxygenation in humans subjected to OLA in the LDP. The effects of dobutamine on

shunt fraction are not the only factors to consider. It is of more relevance to be concerned about the effects of dobutamine on all the components of shunt (i.e. both the amount of blood passing via the shunt *and* the venous oxygen content) when considering the effects of an inotrope on arterial oxygenation.

Oxygen insufflation down the NDL would have ensured that at least a proportion of the NDL's alveoli would have been oxygenated (Rees and Wansbrough 1982b). Increases in cardiac output and PA pressure due to dobutamine and subsequent diversion of blood to the NDL could possibly have resulted in the shunted blood being exposed to alveoli that contained oxygen. Therefore, the effects of the increase in "shunt" may have been limited by this manoeuvre. If this manoeuvre had not been conducted, patients may have experienced a decrease in oxygenation as is observed when patients with low V/Q units who are administered dobutamine (Russell and James 2000).

In the current study, infusions of dobutamine did not increase oxygen consumption. The question as to whether catecholamines increase oxygen consumption by both positive inotropic effects and effects on peripheral tissues has been investigated by Kazai and colleagues. In two of the three studies he and his colleagues have published on the topic, 6 $ug.kg^{-1}.min^{-1}$ of either dopamine or dobutamine were administered during cardiopulmonary bypass while the heart was cross clamped and cardiopleged (Karzai, Lotte et al. 1996; Karzai, Gunnicker et al. 1996). Dobutamine, but not dopamine, increased oxygen consumption by 11%. Bhatt and co-workers studied healthy awake physician volunteers (Bhatt, Hutchinson et al. 1992). Administration of dobutamine 2.5, 5 and 7.5 $ug.kg^{-1}.min^{-1}$ produced an increase in oxygen consumption from 128 ± 6.1 to 159 ± 8 $ml.min^{-1}.m^{-2}$ ($p < 0.05$). It is noteworthy that a linear relationship between oxygen consumption and delivery was seen in this study (Bhatt, Hutchinson et al. 1992). A similar, relationship was observed in the current study (Figure 3.5.6 and 3.5.7). However, the reasons why VO_2 did *not* increase during the administration of dobutamine during OLA in the present study are unclear.

In summary, with regard to oxygen flux during OLA in the dobutamine group, the following results were produced:

6. Induction of anesthesia and the approximately 1^{O} Celsius decrease in temperature induced a 39% decrease in VO_2. However, both cardiac output and oxygen delivery were unchanged during two-lung anesthesia when compared to the awake baseline state. The consequence was an increase in $S\square O_2$ from 75.1% ± 5.7 to 89.9% ± 4.7 and $P\square O_2$ from 5.4 ± 0.5 to 8.6 ± 1.7 kPa during two-lung anesthesia.
7. Initiation of OLA resulted in an increase in cardiac output even before dobutamine was administered. However, no change in VO_2 was noted. This improved the DO_2/VO_2 ratio but resulted in no change in the already high $P\square O_2$ (9.0 ± 1.7 kPa) and $S\square O_2$ (90.6 ± 4.7 %) compared with the values observed during two-lung anesthesia.
8. Dobutamine caused pulmonary vasodilatation.
9. Arterial oxygenation was not improved and neither was shunt worsened by dobutamine administration.

In conclusion, under conditions in the present study, dobutamine administration during OLA did not improve, but maintained the already high venous and arterial oxygenation compared with OLA alone. Therefore the study hypothesis, that dobutamine would induce improvement in RVF and the increase in cardiac output during OLA would improve arterial oxygenation, does not hold in the current study. The hypothesis must therefore be rejected. This is in contrast to the findings of Mathru et al, and Nomoto and Kawamura who demonstrated that inotrope

administration resulted in an increase in arterial oxygenation.

The different results are not at odds with each other. The differences can be explained in the following way. Conditions *in the current study* resulted in a favourable DO_2/VO_2 ratio and a high starting P□O_2. Therefore the venous saturations were on the flat part of the oxygen dissociation curve and on the flat part of the Kelman curve. Further increases in cardiac output and the DO_2/VO_2 ratio would not be expected to, and did not, increase P□O_2, S□O_2, or C□O_2. Thus, arterial oxygenation content and saturation did not change on the increase in cardiac output associated with the administration of dobutamine. In contrast, in the Mathru study, the low starting venous saturations and tensions were improved by increases in the DO_2/VO_2 ratio. As the venous starting point on the oxygen dissociation curve was "low," significant benefit in arterial oxygenation was obtained on increasing cardiac output. These observations are confirmed by Kelman's graphs (Figures 4.4.2.1 and 4.4.2.3).

Another area of concern is that pulmonary vasodilatation caused by dobutamine may result in arterial hypoxemia as exemplified in Russell and James' animal study. However, there is currently no evidence that the administration of dobutamine in dosages of up to 7 $ug.kg^{-1}.min^{-1}$ increases shunt and worsens arterial oxygenation in humans subjected to OLA in the LDP. The vasodilatory effects of dobutamine resulting in a possible increase in shunt fraction are not the only factor to consider when studying its effects on arterial oxygenation. It is of more relevance to be concerned about the effects of a drug on all aspects of the shunt that affect arterial oxygenation (i.e. the shunt fraction *and* the venous oxygen content) when considering the effects of an inotrope on arterial oxygenation.

4.9 Extrinsic and intrinsic PEEP and OLA

The hypothesis to be examined states that PEEP applied to the DL will restore FRC during OLA. This will not only return low V/Q units towards normal with an improvement in arterial oxygenation, but also have salutary effects on PVR and cardiac output (Cohen and Eisenkraft 1996; Cohen, Eisenkraft et al. 1988; Cohen, Thys et al. 1985a; Baehrendtz, Bindslev et al. 1983). PEEP will therefore improve RV performance. Thus, the application of DL PEEP will increase cardiac output and the improved DO_2/VO_2 ratio will advantage tissue, and thereby arterial oxygenation. This concern expressed for both circulation and restoration of low pulmonary V/Q ratios respects the concept of "best PEEP" (Inomata, Nishikawa et al. 1997; Benumof 1991). It was further hypothesised that the decrease in DL PVR induced by PEEP will decrease diversion of blood to the NDL, decrease shunt and improve arterial oxygenation.

4.9.1 NDL $PEEP_5$: hemodynamics, oxygenation and intrinsic PEEP

Surprisingly few studies have concerned themselves with the effect of "small" amounts of PEEP on either hemodynamics or oxygenation during OLA (Capan, Turndorf et al. 1990; Alfery, Benumof et al. 1981; Aalto, Heinonen et al. 1975). Alfery and colleagues demonstrated that in dogs undergoing OLA, the administration of DL $PEEP_5$ compared with ZEEP, favourably influenced both shunt and arterial oxygenation (Alfery, Benumof et al. 1981). Abe and colleagues also demonstrated a beneficial effect on PaO_2 of 4 cm H_2O of PEEP applied to DL. This was unaccompanied by changes in cardiac output or venous oxygen saturation (Abe, Mashimo et al. 1998).

In the current study, the application of 5 cm H_2O PEEPe to the DL did not result in a uniform decrease in the indices of opposition to pulmonary blood flow. There was a 57% decrease in characteristic impedance on administration of

$PEEP_5$ compared to baseline values when the patients were awake. Another index of opposition to pulmonary flow, PA elastance, increased by 25% on application of DL $PEEP_5$ compared to when the patients were awake. However, the application of $PEEP_5$ did not change the indices of opposition to pulmonary flow compared to when OLA alone was being conducted. Neither did the application of $PEEP_5$ improve the indices of RV performance or the parameters of oxygenation compared to the OLA step when external PEEP was not applied. These findings do not support the stated hypothesis of this section. Aalto-Setala and colleagues (Aalto, Heinonen et al. 1975) similarly demonstrated the failure of $PEEP_5$ compared with ZEEP to increase oxygenation or change hemodynamics during OLA in humans undergoing lobectomy. Surely, the application of 5 cm H_2O of PEEP to the DL during OLA would have restored lung volume to close to baseline levels, decreased PVR and resulted in an improved cardiac output and venous and arterial oxygenation in our patients (Cohen 1995; Benumof 1991). In addition, the question needs to be asked why hemodynamics and oxygenation in the $PEEP_5$ step did not differ from OLA when PEEPe was not applied? The answer probably lies therein that intrinsic PEEP exercises a ubiquitous presence during OLA (Ducros, Moutafis et al. 1999; Inomata, Nishikawa et al. 1997; Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996; Bardoczky, d'Hollander et al. 1994; Slinger, Hickey et al. 1989). Levels of PEEPi in the current and other studies were similar in degree to that which was produced by applying 5 cm H_2O PEEPe during OLA.

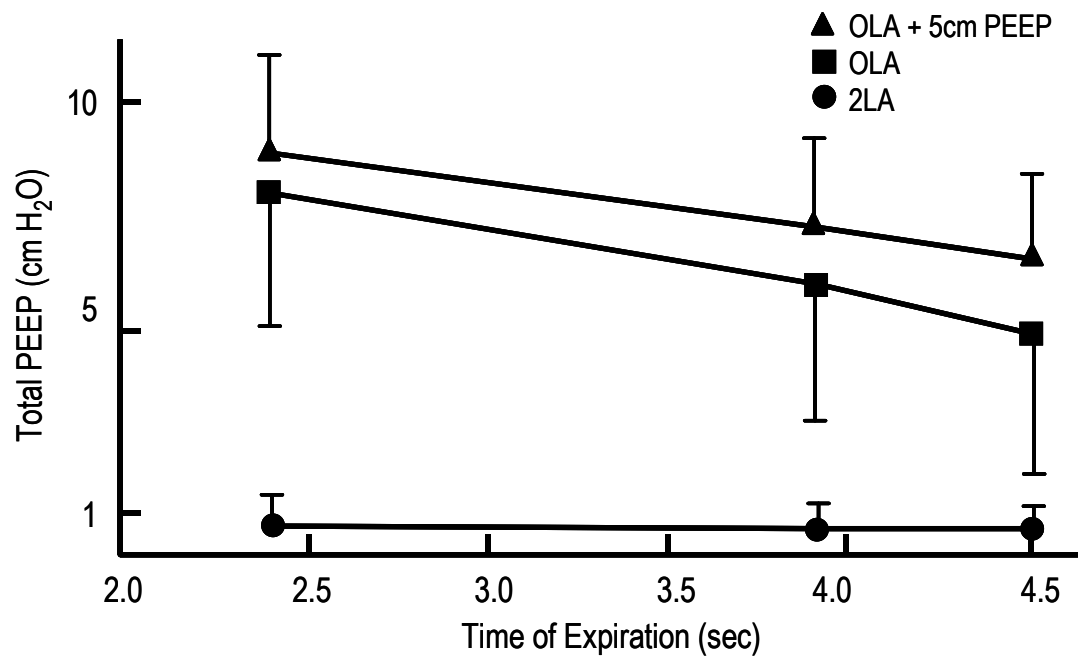

Figure 4.9.1.1

The effects of varying expiratory time on the amount of intrinsic PEEP (indicated by the "total PEEP on the "y axis" in the diagram above) during OLA. Data represented as means and the error bars represent one standard deviation from the mean. Tidal volume was 10 milliliters per kilogram body weight and respiratory rate was 10 breaths per minute during both two and one lung ventilation (OLV) with and without the addition of extrinsic PEEP (OLA + 5 cm PEEP). Measurements were made at expiratory times of 2.4, 3.9 and 4.5 seconds, which correspond, with I:E ratios of 1.5:1, 1:2 and 1:3. The intrinsic PEEP was higher during OLA without extrinsically applied PEEP than during two-lung ventilation (p = 0.001). Furthermore, intrinsic PEEP increased as expiratory time decreased (p = 0.001).

Redrawn from Slinger, Hickey et al, 1998.

Intrinsic PEEP ranged between 3 ± 2.7 to 5 ± 3.1 cm H_2O during OLA in the control group. The development of PEEPi is governed by the ability of the dependent lung to empty the delivered tidal volume by the end of expiration (Rossi, Polese et al. 1995; Tobin and Lodato 1989; Marini, Culver et al. 1985). The factors to be taken into account are:

- Inspired tidal volume,
- The pulmonary time constant which is determined by the product of compliance of the lung and chest wall and resistance to expiration (Slinger and Hickey 1998; Rossi, Polese et al. 1995; Bardoczky, d'Hollander et al. 1994; Simbruner 1986) and,
- The time available for expiration (Slinger, Hickey et al. 1989; Tobin and Lodato 1989).

Each factor needs to be independently addressed. The functioning of the constant flow generator type ventilator employed in the current study (Ohmeda 7700) would not have been significantly impaired by the increased airway resistance attributable to ventilation being conducted via a relatively narrow lumen endotracheal tube during OLA. Thus, the set tidal volume would have been delivered during inspiration irrespective of this increased resistance (Mushin, Rendell-Baker et al. 1980). However, the whole of the delivered tidal volume needs to be expired by the end of expiration to prevent gas retention from occurring (Myles 1996). The tidal volumes delivered in this study were 6 to 7 $ml.kg^{-1}$. These are relatively small compared to conventionally used tidal volumes. This relatively small volume would have limited the development of excessive amounts of PEEPi during OLA (Myles 1996). Yokata and colleagues delivered a tidal volume of 8 $ml.kg^{-1}$ at a breath rate of 12 per minute to the DL (Yokota, Toriumi et al. 1996). These ventilatory settings were close to those that were used to ventilate our patients. They demonstrated similar values of PEEPi (3.2 ± 3.3 cm H_2O) as were observed in the current study. In Inomata's study a tidal volume of 8 $ml.kg^{-1}$ via a left sided 37 French Mallinckrodt® DLT resulted in PEEPi of 4 ± 2 mm Hg (5.32 ± 2.7 cm H_2O). However, this relatively small tidal volume was delivered at a frequency of 16 breaths per minute, which would have limited time available for expiration (Inomata, Nishikawa et al. 1997).

In the current study, the patients were administered a non-depolarising muscle relaxant and moderately high dosages of alfentanil. The patients did not breathe spontaneously and expiration was purely a passive process. Therefore the elastic recoil of the lung and chest wall was the driving force for expiration. The decrease in FRC on induction of anesthesia and the additional decrease in DL volume imposed by the LDP decreases lung compliance (Benumof 1991; Nunn 1990; Klingstedt, Hedenstierna et al. 1990). Such decreases in lung and chest wall compliance will facilitate passive expiration.

On the other hand, in severe COPD, significant destruction of pulmonary elastic tissue occurs. This results in a decrease in the elastic recoil of the lung (Rossi, Polese et al. 1995). Szegedi points out that patients with COPD do not develop decreases in FRC or atelectasis during anesthesia that would decrease compliance and aid lung emptying (Szegedi 2001). It is not surprising therefore, that the amount of PEEPi in this and other studies was inversely related to the severity of COPD (Ducros, Moutafis et al. 1999; Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996).

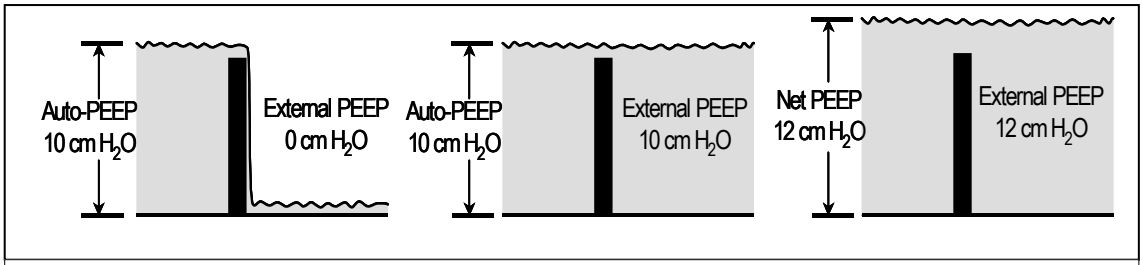

Figure 4.9.1.2 The analogy of a waterfall over a dam wall is used to explain the effect of external PEEP (the downstream pressure) on PEEPi (the upstream pressure) during expiration. Redrawn from Tobin and Lodato, 1989.

Significant relationships between the extent of preoperative lung function impairment and the amount of PEEPi exist in this study. The strongest of these is that between preoperative FEV_1 and intrinsic PEEP during OLA (Table 3.5.6 and Figures 3.5.12, 3.5.13 and 3.5.14). Albeit the strengths of these relationships were relatively weak, they are comparable with those described in other studies (Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996). [#]

What can be established from the above discussion is that 3 to 5 cm H_2O PEEPi occurred in our patients. This amount of PEEPi was related to the preoperative severity of obstructive lung disease. It is not possible to draw conclusions about PEEPi in the dobutamine and PEEP groups because of the small number of subjects (2 in each group) that were studied. There is however no reason to suspect that similar amounts of PEEPi did not occur during OLA in the other groups of the current study.

The poor elastic recoil forces governing expiration in patients with COPD are aggravated by their increased expiratory resistance (Rossi, Polese et al. 1995; Tobin and Lodato 1989). Bardoczky and associates demonstrated that airway resistance was significantly higher during OLA in patients who exhibited PEEPi (2.4 cm $H_2O.l^{-1}.s$) than those who did not (1.7 cm $H_2O.l^{-1}.s$) (Bardoczky, d'Hollander et al. 1994). Factors influencing airway resistance during OLA include the patient's own airway, DLT lumen, DLT connectors and breathing circuit resistance. These factors explain the presence of PEEPi that occurs even in patients with *normal* lung function during OLA (Inomata, Nishikawa et al. 1997; Bardoczky, d'Hollander et al. 1994). It is also important to note that a certain amount of PEEP is attributable to the expiratory valve on the Ohmeda 7700 ventilator that was used in the current study. Further investigations indicated that a constant pressure gradient of 2 cm H_2O over the Ohmeda expiratory valve exists at a range of flows from 1 to 10 litres per minute.

An increase pulmonary resistance in the presence of an increased lung compliance will increase the amount of time needed to empty a tidal volume delivered to the DL. When delivering a tidal volume of 10 $ml.kg^{-1}$ and while varying the expiratory time during OLV, Slinger demonstrated that the time available for expiration largely determined the amount of intrinsic PEEP present (Slinger, Hickey et al. 1989) (Figure 4.9.1.1). Tidal volumes of 6 to 7 $ml.kg^{-1}$ at

[#] It is noteworthy that a PEEPi of 9.5 cm H_2O was measured on two occasions during OLA in one of the patients in the dobutamine group who demonstrated severe obstructive airway disease on his preoperative LFT's. FEV_1 was 48% of predicted, FEV_1/FVC 61%, FEF50 18%, FEF75 8% and ITGV determined by pletysmography 184% of predicted for the patient's age, weight and sex.

respiratory rates of 12 breaths per minute and an I:E ratio of 1:2 were typically employed in the current study. These ventilatory settings resulted in an expiratory time of 3.3 seconds. The resultant levels of PEEPi do not differ from those observed during similar expiratory times in Slinger's study (Slinger, Hickey et al. 1989).

It is remarkable that neither hemodynamics nor oxygenation differed between the $PEEP_5$ step and the OLA step when external PEEP was not applied. The question that arises is what is the relationship between PEEPe and PEEPi? Tobin and Lodato discuss the interaction of PEEPi and PEEPe in terms of a waterfall effect (Figure 4.9.1.2) (Tobin and Lodato 1989). They suggest that externally applied PEEP less than or equal to intrinsic PEEP has no effect on intrinsic PEEP. Only when externally applied PEEP exceeds intrinsic PEEP, is there an effect on the lung itself. However, Rossi and colleagues caution that until a "*critical value of somewhat lower than the PEEPi*," is reached, external PEEP will not add to intrinsic PEEP (Rossi, Polese et al. 1995). This means that application of PEEPe equal to the initial PEEPi will induce a moderate increase in FRC. Only values of PEEPe less than 75 to 85% of PEEPi will not significantly increase the end-expiratory volume (Rossi, Polese et al. 1995). Therefore Slinger and Hickey applied external PEEP in similar amounts to the PEEPi observed during OLA. This resulted in an increase in PEEPi of 1 to 2 cm H_2O (Slinger and Hickey 1998; Slinger, Hickey et al. 1989). Inomata and colleagues studied humans in the lateral decubitus position undergoing OLA. They first determined PEEPi and then applied external PEEP equal to PEEPi. This should, if Tobin and Lodato's "waterfall theory' is correct, not have made any difference to shunt, PVR, oxygen delivery, or arterial oxygenation (Tobin and Lodato 1989). However, application of the equivalent amount of PEEP to the PEEPi present resulted in these parameters improving to the best levels observed in their study. Application of a further 5 cm H_2O PEEP above PEEPi impacted unfavourably on these parameters. Their study is interesting and needs to be viewed in the light that the critical end-expiratory pressure below which PEEPe would not increase FRC was probably exceeded in the Inomata study.

The aforementioned observations contain the reasons why no difference in oxygenation or hemodynamics was seen with $PEEP_5$ during OLA. A significant amount of intrinsic PEEP is universally present during OLA (Slinger, Kruger et al. 2001; Ducros, Moutafis et al. 1999; Bardoczky, d'Hollander et al. 1998; Inomata, Nishikawa et al. 1997; Bardoczky, Yernault et al. 1996; Yokota, Toriumi et al. 1996; Bardoczky, d'Hollander et al. 1994; Slinger, Hickey et al. 1989). The levels of extrinsic PEEP in the $PEEP_5$ step do not differ from the levels of PEEPi during OLA in the current or other studies (Rossi, Polese et al. 1995; Slinger, Hickey et al. 1989; Tobin and Lodato 1989). Therefore, the presence of intrinsic PEEP will limit the effects of similar amounts of externally applied PEEP: small differences between PEEPe and PEEPi will have modest if any impact on oxygenation or hemodynamics

The concern that the use of small tidal volumes may however lead to progressive decreases in lung volume during OLA is expressed by various authorities and demonstrated by Khanam and Branthwaite (Cohen 1995; Benumof 1991; Capan, Turndorf et al. 1990; Flacke, Thompson et al. 1976; Khanam and Branthwaite 1973). Such decreases in FRC and the subsequent development of low V/Q units may be counteracted by the presence of either intrinsic PEEP or the application of PEEPe (Inomata, Nishikawa et al. 1997; Myles 1996; Capan, Turndorf et al. 1990). Hedenstierna and colleagues studied patients subjected to OLA in the LDP using a tidal volume of 10 $ml.kg^{-1}$ when ZEEP or $PEEP_{10}$ was applied to the DL (Klingstedt, Hedenstierna et al. 1990). Using computerized tomography, they demonstrated that PEEP10 results in complete (3 of 8 patients) or partial (5 of 8 patients) elimination of DL

atelectasis. Therefore the presence of PEEPi is a likely reason why the small tidal volumes employed in the current study did not result in progressive decreases in arterial oxygenation (Benumof 1991; Capan, Turndorf et al. 1980; Kerr, Smith et al. 1974; Das, Fenstermacher et al. 1970).

Evidence of the benefit of intrinsic PEEP is contained in Myles's analysis of Yokota and colleagues' study (Myles 1996). This analysis indicated that PEEPi maintains DL volumes and benefits arterial oxygenation during OLA. Nonetheless, Bardoczky and colleagues have demonstrated an inverse relationship between intrinsic PEEP and PaO_2 during OLA. This emphasises that too much of a good thing can be problematic (Bardoczky, d'Hollander et al. 1998). Deleterious effects of intrinsic PEEP are also seen in patients with very low levels of lung elastic recoil. They tend to develop dynamic hyperinflation during OLA. This may lead to volotrauma (Sivalingam and Tio 1999; Slinger 1999; Williams, Evans et al. 1996) or life threatening hemodynamic compromise (Sivalingam and Tio 1999; Conacher 1998; Myles, Ryder et al. 1997; Myles, Madder et al. 1995; Quinlan and Buffington 1993; Myles and Weeks 1992).

Another issue of importance is whether $PEEP_5$ during OLA will be effective in restoring lung volume to preoperative levels. Slinger and colleagues have demonstrated that on the application of $PEEP_5$ to the DL, if the difference between the lower inflexion point and the end-expiratory pressure plateau becomes negative, lung volume probably increases (Slinger, Kruger et al. 2001). The aforementioned scenario was associated with an increase in arterial oxygenation during OLA. However, from Slinger and colleagues' data, it is apparent that the effect of $PEEP_5$ on lung volume is unpredictable in individual patients. In other words, in other subjects in the same study, the application of $PEEP_5$ did not result in increases in lung volume or arterial oxygenation during OLA (Slinger, Kruger et al. 2001). Rothen and colleagues have demonstrated that an airway pressure of 20 cm H_20 sustained for 15 seconds was necessary to start recruitment of lung that had become atelectatic during two-lung anesthesia in the supine position (Rothen, Sporre et al. 1993). A sustained airway pressure of 40 cm H_20 was needed to almost completely reverse the atelectasis associated with anesthesia (Rothen, Sporre et al. 1993). Tusman and colleagues attempted to restore lung volume and arterial oxygenation during OLA by administering a peak airway pressure of up to 40 cm H_20 and PEEP of 20 cm H_2O for 10 respiratory cycles (Tusman, Bohm et al. 2002). A tidal volume of $8ml.kg^{-1}$ and 100% oxygen was administered during the recruitment manoeuvre. The recruitment manoeuvre was administered after the PA to the lobe being resected had been clamped. Both DL and the remaining NDL segments were included in the recruitment manoeuvre. The patients were thereafter returned to the OLA state and arterial oxygenation measured 15 minutes later. The blood gas during the second period of OLA demonstrated a PaO_2 similar to that seen during two-lung anesthesia that was significantly higher than that seen during OLA. The conclusion of this study was that a recruitment manoeuvre improves arterial oxygenation during OLA (Tusman, Bohm et al. 2002). However, this study does not unequivocally answer the question whether recruitment manoeuvres are successful to restore arterial oxygenation during OLA. Firstly, both lungs were recruited in the Tusman study. The authors defend this problem by suggesting that recruitment of the NDL would not helpful in restoring arterial oxygenation as all oxygen in the NDL alveoli would have been absorbed within 5 to 7 minutes and quote an article authored by Rothen and colleagues to support their argument (Rothen, Sporre et al. 1995). It may also be speculated that similar amount of atelectasis would have occurred in the DL within the same period of time (Rothen, Sporre et al. 1995; Rothen, Sporre et al. 1995a). However, this study does not convincingly answer the question whether recruitment of the DL alone

improves arterial oxygenation. Secondly, Tusman and colleagues also suggest that a more pronounced HPV response may occur after repeated periods of hypoxia. This argument detracts from their contention that recruitment itself improves oxygenation during OLA. Therefore, it appears as if the methodology used in this study does not conclusively address the question of whether a recruitment manoeuvre improves arterial oxygenation during OLA.

In summary, when $PEEP_5$ was applied to the DL during OLA in the current study:

4. Right ventricular function, hemodynamics, oxygen flux nor arterial oxygenation was affected by the application of $PEEP_5$ compared to the step when no external PEEP was applied.
5. Significant amounts of intrinsic PEEP were present during OLA in the control group patients. The degree of intrinsic PEEP was weakly related to the derangement in preoperative LFT's.
6. The most likely reason why $PEEP_5$ did not make a difference to oxygenation or hemodynamics is the existence of similar amounts of intrinsic PEEP during OLA. These findings confirm Myles's contention that low levels of intrinsic PEEP may have salutary effects on oxygenation during OLA (Myles 1996).

Therefore the study hypothesis that administration of PEEP to the DL improves its FRC, that restores low V/Q ratios and PVR thereby improving RV function and systemic and arterial oxygenation has to be rejected with regard to the administration of $PEEP_5$ to the NDL

4.9.2 NDL $PEEP_{10}$ during OLA

Unfortunately, only 7 subjects were enrolled in the $PEEP_{10}$ step. Consequently, intragroup comparisons at times approached, but did not reach, statistical significance. This was in spite of a clinical difference being suspected. Therefore, because of the small number of subjects included in the $PEEP_{10}$ step, real differences may have been missed, or in other words, a beta error may have been incurred (Coetzee 2001).

	ZEEP	DL $PEEP_9$	DL $PEEP_{10}$	DL $PEEP_{16}$
Blood flow to NDL as % of total cardiac output	43	50	55	65
Blood flow to DL as % of total cardiac output	57	50	45	35

Table 4.9.2.1 Data from Hedenstierna and colleagues study (Hedenstierna, Baehrendtz et al. 1984). PEEPe is measured in cm H_2O.

During the application of 10 cm H_2O PEEP to the DL, pulmonary arterial elastance and resistance was greater than values calculated for two-lung anesthesia and one lung anesthesia without application of extrinsic PEEP (Table 3.3.3.12). Inomata also observed increases in PVR when higher levels of PEEP are delivered to the DL (Inomata, Nishikawa et al. 1997). Hedenstierna and colleagues conducted an elegant study in patients without clinical, ECG or roentographic signs of cardiopulmonary disease comparing the effects of PEEPe and ZEEP during one and two-lung anesthesia in the lateral decubitus position (Hedenstierna, Baehrendtz et al. 1984). They described the distribution of pulmonary perfusion when varying amounts of PEEP were applied to the DL. During IPPV to both lungs without

PEEPe, the cardiac output was distributed so that 57% went to the DL and 43% to the NDL. On application of 9 cm H_2O PEEP to the DL, the distribution of pulmonary blood flow to each lung did not differ. However, on application of 10 and 16 cm H_2O PEEP to the DL, perfusion to that lung decreased to 45 and 35% respectively. The mechanism involves an increase in lung volume of the DL to such a degree that lung volume exceeds FRC and alveolar vessel compression occurs which increases pulmonary vascular resistance.

The indices of RV performance (RVSWI, RVEF) were unchanged during OLA in the $PEEP_{10}$ step (Table 3.3.3.15). However, stroke volume decreased during $PEEP_{10}$. This is remarkable as only one other change in SV was recorded in either the control or the dobutamine groups. The 25% decrease in cardiac index from the $PEEP_5$ to the $PEEP_{10}$ epochs creates the suspicion that $PEEP_{10}$ decreased cardiac output: nonetheless, statistical analysis indicated that this was not statistically significant. This lack of a significant difference is most likely due to a type 2 or beta error referred to at the beginning of this section. The question can be asked whether this decrease in stroke volume is clinically significant? The answer is that the cardiac indices and stroke volumes in this study were relatively "high". "High" here indicates that these cardiac indices and stroke volumes at baseline were significantly above the inflexion point of the "Kelman and Nunn" curve (Figure 4.4.2.3). A $PEEP_{10}$ induced 25% decrease in stroke index (or cardiac index if it had occurred) would not have resulted in circulatory or oxygenation on the basis of a decrease in venous oxygenation. However, in another group of patients, with hemodynamics that are more marginal, a 25% decrease in cardiac output may cause problems with venous and thus arterial oxygenation.

RVEDVI did not change from baseline during the control, dobutamine, or $PEEP_5$ groups. However, administration of 10 cm H_20 PEEP to the DL resulted in RVEDVI decreasing by 25% from baseline (Table 3.3.3.11). Similar magnitudes of decreases in RVEDVI with $PEEP_{10}$, have been reported during two-lung ventilation (Groeneveld, Schreuder et al. 1990; Assmann and Falke 1988; Eddy, Rice et al. 1988; Biondi, Schulman et al. 1988; Baehrendtz, Bindslev et al. 1983).

It is apparent that right ventricular SV was deleteriously affected by these excessive levels of PEEP for two reasons: firstly the increase in PVR and secondly the decrease in end-diastolic volume of the RV. Which of these two factors dominated this scenario? Albeit PVR increased by 33% during the administration of $PEEP_{10}$ and attained the highest levels recorded in this study, similar orders of magnitude of increase in opposition to pulmonary flow have been shown not to impair RV performance. Fourie demonstrated that PA pressure has to increase to more than 250% of baseline before RV performance even begins to be compromised (Fourie 1989). In conclusion, the significant finding of this study is that $PEEP_{10}$ results in a decrease in right ventricular preload. The normal RV acts as a preload dependent flow pump (Conrad 2001; Hennebry and Gerstenblith 2001; Nelson, Safcsak et al. 2001; Boldt, Kling et al. 1990) and $PEEP_{10}$ impairs its ability to deliver a stroke volume. Only at higher levels of PEEP (15 to 20 cm H_2O) do severe increases in PVR result to the extent that RV afterload is significantly affected (Rossi, Polese et al. 1995).

The decrease in SV with the application of PEEP was accompanied by a decrease in oxygen delivery. Oxygen delivery achieved its minimum and maximum levels respectively during OLA with $PEEP_{10}$ and without PEEPe (Table 3.3.3.16). The administration of $PEEP_5$ or $PEEP_{10}$ did not affect oxygen consumption. Thus, the ratio of oxygen delivery to consumption decreased. This resulted in both mixed venous saturation and tension decreasing to their

lowest levels (79.0 ± 9.4 % and 7.0 ± 1.9 kPa respectively) during OLA. The consequence was that the proportion of oxygen extracted by the tissues rose to the highest fraction (OER = 0.20) seen in any group during anesthesia albeit, statistical significance was not achieved (p = 0.066). The arterio-venous oxygen content difference also increased to its highest level during OLA with the application of $PEEP_{10}$. This implies that systemic oxygenation declined to its lowest margin of safety during OLA, albeit these levels of oxygenation were still far in excess of the human metabolic requirements during anesthesia. The decrease in PaO_2 to 25.3 ± 16.1 kPa with administration of $PEEP_{10}$ was of minimal clinical significance, as oxygen saturation never decreased below 95.7 ± 7.7 %. However, if the large safety margin induced by the decrease in VO_2 produced by this particular anesthetic technique had not been present, and these patients had not been operating from a baseline that had plenty of reserve, $PEEP_{10}$ could conceivably have threatened both tissue and arterial oxygenation. This decrease in oxygenation during the $PEEP_{10}$ epoch is reflected by the relationship between cardiac index and CaO_2 now being on a much steeper part on the Kelman curve (Figure 4.4.2.3).

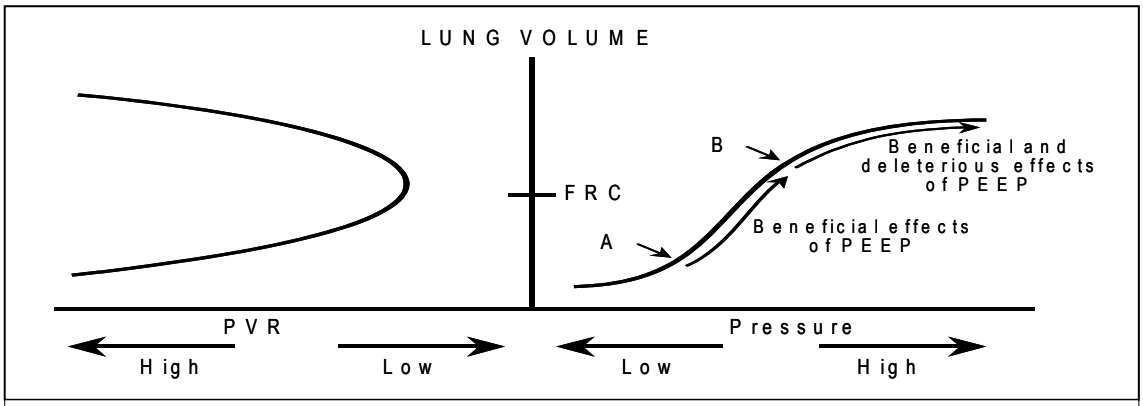

Figure 4.9.2.1 The therapeutic index for PEEP during OLA is illustrated by juxtaposition of pulmonary compliance and PVR-lung volume curves. A. If the FRC of the DL is low, addition of PEEP will decrease PVR. B. If the DL volume is however increased by the application of PEEP, this may start having deleterious effects on lung volume and PVR. This emphasizes the need for a measure of DL volume during OLA. Redrawn from Capan, Turndorf and Miller, 1990.

A further contribution to decreased arterial oxygenation with the application of $PEEP_{10}$ to the DL could be an increase in DL PVR. This would have had the effect of diverting blood to the NDL (Hedenstierna, Baehrendtz et al. 1984). That arterial oxygenation decreased during $PEEP_{10}$ with potential increase in diversion of blood to the NDL, lends support to observations that oxygen insufflation to the NDL did not improve oxygenation. Capan and colleagues observed that oxygen insufflation down the NDL while $PEEP_{10}$ was administered to the DL did not benefit arterial oxygenation (Capan, Turndorf et al. 1980).

This deleterious effect of $PEEP_{10}$ on the RV also had a spill over effect on the systemic circulation. Mean arterial blood pressure (MAP) deteriorated during OLA when both 5 and 10 cm H_2O DL PEEP was applied (Table 3.3.3.17). This decrease in MAP did not exceed 25% during either level of PEEP. This is a clinically tolerable decrease. However, hypotension presented a clinical problem in individual patients in whom systolic pressure decreased by as much as 55 to 65% in the $PEEP_5$ and $PEEP_{10}$ groups respectively. For example, in one of the patients who demonstrated a severe decrease in MAP, RVEDVI fell to 69 $ml.m^{-2}$ and PVR was 180 $dynes.secs.cm^{-5}$. In another

individual who became severely hypotensive, severe preoperative hyperinflation was present on preoperative LFT's (intrathoracic gas volume measured by body plethysmography was 180% of predicted). This observation prompted an investigation of the relationship between intraoperative hypotension and the preoperative ITGV. However, no relationship was evident between these two variables (Table 3.5.7). The 25% decrease in MAP during PEEP administration could also elicit concern about RV coronary perfusion pressure. RV coronary perfusion pressure[#] was 78.3 mm Hg when the patients were awake and 66.6 mm Hg during OLA without PEEP. These values fell to 48.9 and 49.4 mm Hg with $PEEP_5$ and $PEEP_{10}$ cm H_2O respectively (Table 3.3.3.17). In spite of this decrease in RV coronary perfusion pressure, no evidence of ischemic RV dysfunction was present as evidenced by a lack of changes in the ECG or hemodynamic parameters (CVP, RVEDVI or RVEF). These levels of RV coronary perfusion pressure are higher than the pressures at which circulatory collapse occurred in experimentally produced increases in PVR (Vlahakes, Turley et al. 1981). Furthermore, the predominant reason for the circulatory impairment in the patients enrolled in the current study was a decrease in preload. This decrease in RVEDV probably decreases wall tension so that RV myocardial oxygen demand did not increase.

DL $PEEP_{10}$ has been shown to produce divergent effects on oxygenation (Capan, Turndorf et al. 1990). Most studies demonstrated a decrease or no change in arterial oxygenation on administration of $PEEP_{10}$ (Cohen, Eisenkraft et al. 1988; Katz, Laverne et al. 1982; Capan, Turndorf et al. 1980; Aalto, Heinonen et al. 1975; Tarhan and Lundborg 1970). Why, in the current and other studies, do increasing levels of PEEP not produce uniform and progressive effects on parameters of circulation and oxygenation as demonstrated by Inomata and colleagues? One of the inclusion criteria in the Inomata study was that their patients had to have 'normal' lungs preoperatively. An important factor that is often not considered is the diversity of pre-and intraoperative lung pathology to which a uniform mode of therapy is applied. Cohen and co-workers shed light on this when they demonstrated that DL $PEEP_{10}$ improved oxygenation in patients with PaO_2 values of less than 10.6 kPa (Cohen and Eisenkraft 1996; Cohen 1995; Cohen, Thys et al. 1985b). They attributed this to restoration of the DL FRC in those patients in whom intraoperative DL volume was low (Figure 4.9.2.1). They postulated that this had the effect of optimising DL PVR and thereby less blood was diverted to the NDL (Cohen and Eisenkraft 1996; Cohen, Thys et al. 1985a; Cohen, Thys et al. 1985b). This can be seen by the shunt fraction decreasing from 42 ± 8 to 31 ± 17 % on application of $PEEP_{10}$ to the DL in Cohen et al's study.

One aspect that Cohen did not highlight in his paper was the influence of PEEP on cardiac output and cellular oxygenation during OLA. On inspection of the data in their paper (Table 4.9.2.2), the decrease in cardiac output that they observed with DL $PEEP_{10}$ was not accompanied by a decrease in $S\square O_2$ as occurred in our study. Kelman and colleagues predict that the deleterious effects of PEEP on cardiac output will negatively affect CaO_2 in the presence of a large shunt (Kelman, Nunn et al. 1967).

[#] RV coronary perfusion pressure was shown by Cross to be " the planimetrically measured difference between the pressure in the ascending aorta and the RV pressure" (Cross 1961). He demonstrated, using this method in the non-distended canine RV with a pressure of less than 5 mm Hg, that "right coronary flow was linearly related to the mean right coronary driving (perfusion) pressure". In the absence of the ability to do planimetry, it was considered reasonable to use the difference between mean systemic arterial and mean PA pressures as an index of RV coronary perfusion pressure.

Thus, the hypothesis that administration of PEEP to the DL improves its FRC, restores low V/Q ratios and PVR and thereby improves RV function and systemic and arterial oxygenation is rejected.

The effects of PEEP on hemodynamics and oxygenation during OLA may be summarised as follows:

1. In patients with a significant decrease in DL volume during OLA, the application of the ideal amount of PEEP will lead to the optimisation of FRC. This will decrease venous admixture occurring in the DL. Furthermore, optimisation of DL volume will decrease PVR and PAP, and less blood will be diverted to the NDL. These mechanisms will decrease shunt in the subgroup of patients experiencing a decrease in DL volume. This has been seen in both the Cohen and Inomata studies (Inomata, Nishikawa et al. 1997; Cohen and Eisenkraft 1996). In the current study, intrinsic PEEP (3 ± 3 cm H_2O) appears to result in a lung volume that had no deleterious effects on PVR, the RV and the circulation. $PEEP_5$ was almost indistinguishable from OLA without external PEEP in these regards.
2. However, greater (excessive) amounts of PEEP may have deleterious cardio-respiratory effects. $PEEP_{10}$ commonly leads to decreases in stroke volume, as seen in our study, and cardiac output, as seen in Cohen and colleagues' study (Cohen and Eisenkraft 1996). This decrease in cardiac output is predominantly due to a decrease in preload, as PVR does not increase to levels that are known to impair RV performance. The decrease in the DO_2/VO_2 ratio that is induced by excessive PEEP, predictably decreases P□O_2 and can potentially lead to impairment of arterial oxygenation.
3. Increases in DL PVR will divert pulmonary blood flow to the NDL and increase shunt. Oxygen insufflation down the NDL during DL $PEEP_{10}$ does not appear to oxygenate this diverted blood (Capan, Turndorf et al. 1980).

The take home message is that optimising DL volume will play a crucial role in determining arterial oxygenation (Conacher 1997; Cohen, Eisenkraft et al. 1988). The therapeutic index for PEEP is narrow and the anesthesiologist needs to know firstly when the lung volume of the DL approaches FRC and secondly, how to avoid dynamic hyperinflation of that lung (Inomata, Nishikawa et al. 1997). There are multiple ways to address this problem:

1. From the beginning of OLA, ventilation practices need to be adapted according to the pathology of the lung that is being ventilated (Bardoczky, d'Hollander et al. 1998; Bardoczky, Yernault et al. 1996). The physician should study the characteristics of the lung to be ventilated during OLA before surgery commences. Optimal levels of DL PEEP during OLA for patients with normal lungs most likely lie between 3 to 8 cm H_2O (Abe, Shimizu et al. 1998; Inomata, Nishikawa et al. 1997).

2. However, "correct approaches" to the problem do not guarantee that DL volume will be normalised. The interaction of different lung pathologies and intrinsic PEEP during OLA result in small safety margins for both PEEPe and PEEPi (Benumof and Alfery 2000; Benumof 1991). Monitoring methods need to be developed to determine how much PEEPe needs to be applied to restore lung volume. The same monitoring should inform decisions whether excessive amounts of PEEPi are developing that require lengthening of the expiratory time, a decrease in inspired tidal volume and the allowance of (further) hypercapnia. Monitoring could take one or more of the following forms

a. The ideal would be if lung volume could be measured continuously during OLA. Options include:
    i. Stenqvist, Olegard and colleagues have described a method for FRC *monitoring* based on quantification of oxygen consumption and carbon dioxide production during a short apnea. End-tidal (approximately alveolar) oxygen and carbon dioxide concentrations were measured before and after a short apnea of 8 to 12 seconds. FRC was calculated according to standard washin/washout formulas (Stenqvist, Olegard et al. 2002).
    ii. Fretchner and colleagues have described a method of using washin and washout of nitrogen to determine FRC in mechanically ventilated patients in the intensive care unit (Fretschner, Deusch et al. 1993).

b. The continued occurrence of dependent lung flow just before the next inspiration commences indicates that not enough time has elapsed to allow for the completion of expiration. This can be determined in one of two ways:
    i. The display of flow-volume loops to determine whether expiration is complete before a new breath is delivered has recently been reported during OLA (Szegedi 2001; Bardoczky, d'Hollander et al. 1994) and,
    ii. The display of a graph of flow versus time can also determine that expiratory flow is sill occurring at the time the next inspiration starts.

c. Measuring intrinsic PEEP using pressures at the distal (patient) end of the DLT could provide an indication of whether PEEP was present at the end of expiration.

d. Pressure-volume loops could indicate autoPEEP in the following ways:
    i. The pressure in the airways at the end of expiration did not return to zero.
    ii. Either a flattening of the slope at the *top* end of the pressure-volume loop or a decrease in the slope of the pressure-volume loop as bigger tidal volumes are administered indicate that compliance is decreasing due to over distension of the ventilated lung.
    iii. Titrating PEEP to a value at or slightly above the inflexion point on the pressure-volume loop (the so-called “open-lung” approach to ventilation) has been suggested to optimise low lung volumes (Mergio, Volpi et al. 2001).

e. Ventilatory rate can be adjusted by measuring the (average) time constant of expiration. (This measurement would assume that expiration was a monoexponential process and that expiration of most lung units is represented by the dominant time constant). Using this time constant, the time needed to empty the lung of a predetermined percentage of the inspired volume could be calculated. For instance, in Slinger and Hickeys study of PEEP and intrinsic PEEP during OLA (Slinger and Hickey 1998), they reported that the time constant during OLA was 0.8 $\pm$ 0.5 seconds. Using such information, the anesthesiologist could then determine the expiratory time period needed to permit a certain percentage of the tidal volume that is expired. After a period of time equal to three or four time constants, expiration of the previous breath (if inspiration occurred from FRC) would be 95% or 98.2% complete. Using data from the Slinger study, 3.2 $\pm$ 2 seconds would need to be permitted during OLA for 98.2% of the previous breath to be

exhaled. The problem with this approach is that the "air-trapping" would be progressive and the amount of gas above FRC in the ventilated lung would be difficult to determine.

f. Static compliance can be measured pre- and intraoperatively. Maintaining similar static compliance levels intraoperatively by adjusting ventilation to develop or prevent PEEPi, or applying PEEPe, may provide some answers to this vexing problem.

g. The difference between arterial and end-tidal carbon dioxide partial pressures (a-ET PCO_2) has been used to determine optimal levels of PEEP. At optimal PEEP levels, lung volumes and, oxygenation were optimal; the lung was ventilating at the inflexion point of the pressure-volume curve. It was demonstrated that at this level of PEEP, the a-ET PCO_2 difference reaches its lowest level. This approach has been used to titrate PEEP with the aim of optimising lung volume in patients with ARDS (Blanch, Fernandez et al. 1987).

	2LA		OLA		OLA + $PEEP_{10}$		Differences, if any, between OLA
	□	SD.	□	SD.	□	SD.	
PaO_2 (kPa)	26.5	9.0	8.6	0.9	11.5	4.0	$p < 0.05$
Qs/Qt (%)	11.0	6.0	42	8.0	31	17	$p < 0.05$
CO (litres.min^{-1})	3.2	0.6	4.6	1.0	3.9	1.0	$p < 0.01$
MAP (mm Hg)	87.0	11.0	81.0	14.0	84.0	10.0	Not significant
S□O_2 (%)	83.0	8.0	78.0	9.0	77.0	7.0	Not significant

Table 4.9.2.2 Oxygenation and hemodynamic data for patients with PaO_2 < 10.6 kPa on OLA. Adapted from (Cohen and Eisenkraft 1996). Data has been normalized for BSA. BSA was calculated from length and weight data presented in the paper. Values are mean (□) and ± standard deviation). In this select group of patients, $PEEP_{10}$ improved DL FRC and decreased venous admixture with beneficial effects on shunt and arterial oxygenation. $PEEP_{10}$ decreases cardiac output but does not deleteriously affect S□O_2. 11 subjects were included in the study and Student's-t test was used to compare the groups.

3. Occult sources of PEEP need to be considered such as
   a. Patient airway resistance due to bronchospasm and dynamic airway collapse,
   b. Resistance from DLT tube and,
   c. PEEP from the ventilator expiratory valve.
4. Furthermore, the normality of the $PaCO_2$ is not the aim of the game during OLA. Maintaining acceptable lung volume with acceptable oxygenation and hemodynamics while permitting hypercapnia if needed are the important considerations during OLA.

5. Appendices

5.1 Abbreviations

σ	wall stress
□	(pronounced "x – bar"), the mean of a sample
τ	time constant, tau
2 Lung Anes	anesthesia while two-lungs are being ventilated
AC	alternating current
ALI	acute lung injury
Anes	anesthesia
ANOVA	analysis of variance
Ao	aortic or aorta
ARDS	adult respiratory distress syndrome
B.E.	base excess (a negative value represents a base deficit)
BSA	body surface area
C(a-□)O_2	arterio-venous oxygen content difference
C□O2	oxygen content of mixed venous blood
CaO_2	oxygen content of arterial blood
CBF	coronary blood flow
CcO2	oxygen content of pulmonary capillary blood
CI	cardiac index ($l.min^{-1}.m^{-2}$)
Cm H_2O	centimetres of water
CO	cardiac output ($l.min^{-1}$)
Control	control group
COPD	chronic obstructive pulmonary disease
Cp_{50}	plasma concentration needed to provide a 50% chance of suppressing increases of heart rate and blood pressure in response to skin incision (compare to MAC BAR)
CPP	coronary perfusion pressure
CVP	central venous pressure
DAP	diastolic arterial pressure (systemic)
DC	direct current
DL	dependent lung
D_LCO	diffusion capacity for carbon monoxide
D_LCO/Va	diffusion capacity for carbon monoxide corrected for alveolar volume
DLT	double lumen tube
DO_2	oxygen delivery
DO_2I	oxygen delivery indexed for body surface area
DPAP	diastolic pulmonary artery pressure

dPdt	maximum positive rate of rise of left ventricular pressure (mmHg.sec^{-1})
dPdt –	maximum negative rate of decline of left ventricular pressure (mmHg.sec^{-1})
E(t)	elastance at a particular time, t
Ea	effective arterial elastance
ECG	electrocardiograph or electrocardiogram
EDP	end-diastolic pressure
EDV	end-diastolic volume
EEO	end expiratory occlusion
Ees	ventricular end systolic elastance
EF	ejection fraction
E_{max}	maximal ventricular elastance
ERV	expiratory reserve volume
ESPVR	end-systolic pressure-volume relationship
FEF25	forced expiratory flow rate at the time of the FVC is 25 % complete
FEF75	forced expiratory flow rate at the time of the FVC is 75 % complete
F_EO_2	fractional concentration of oxygen (expired)
FEV_1	forced expiratory volume in one second
FEV_1/FVC	the ratio of forced expiratory volume in one second to the forced vital capacity
FiO_2	fractional concentration of oxygen (inspired)
FRC	functional residual capacity
FRC	functional residual capacity
FVC	forced vital capacity
g	gram
$HCO3^-$	bicarbonate concentration
HKT	hematocrit
HPV	hypoxic pulmonary vasoconstriction
HR	heart rate
IAA	inhalation anesthetic agent
IPPV	intermittent positive pressure ventilation
IRV	inspiratory reserve volume
ITGV	intrathoracic gas volume
ITGV	intrathoracic gas volume.
kg	kilogram
kPa	kilopascal(s)
LAP	left atrial pressure
LDP	lateral decubitus position
LFT	lung function test
LV	left ventricle
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume

LVSW	left ventricular stroke work
LVSWI	left ventricular stroke work index
m	metre
MAC	minimal alveolar concentration
MAC (BAR)	minimal alveolar concentration needed to obtund the hemodynamic response to a noxious stimulus
MAP	mean arterial pressure (mmHg)
min	minute
ml	millilitre
mmHg	millimetres of mercury
MPAP	mean pulmonary artery pressure
MVO_2	myocardial oxygen consumption
n	number of subjects
NDL	non-dependent lung
NO	nitric oxide
NYHA	New York Heart Association
^{O}C	degrees Celsius
^{o}C	degrees Celsius
ODC	oxygen dissociation curve
OER	oxygen extraction ratio
OLA	one lung anesthesia
OLV	one lung ventilation
P	pressure
p	probability
$P\square CO_2$	partial pressure of carbon dioxide in mixed venous blood
$P\square O_2$	mixed venous oxygen tension
$P\square O_2$	partial pressure of oxygen in mixed venous blood
P_{50}	the partial pressure of oxygen at which hemoglobin is 50% saturated
P_A	alveolar pressure
PA	pulmonary artery
PA Pes	pulmonary artery pressure at end systole
PAC	pulmonary artery catheter
P_ACO_2	partial pressure of carbon dioxide in alveoli
$PACO_2$	partial pressure of carbon dioxide in alveoli
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
P_AO_2	partial pressure of oxygen in alveoli
PAP	mean pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
P_B	barometric pressure of atmosphere

PcO_2	pressure of oxygen in the pulmonary capillary
PcO_2	partial pressure of oxygen in pulmonary venous capillaries
$PEEP_{10}$	positive end expiratory pressure of 10 cm H_2O
$PEEP_{10}/CPAP_{10}$	positive end expiratory pressure of 10 cmH2O to the dependent lung, and constant positive airway pressure of 10 cmH2O to the non- dependent lung
$PEEP_5$	positive end expiratory pressure of 5 cmH2O
PEEPe	extrinsically applied positive end expiratory pressure
PEEPi	intrinsic positive end expiratory pressure
PEFR	peak expiratory flow rate
Pes	end systolic pressure
PH_2O	partial pressure of water vapour
pHa	the negative logarithm of the hydrogen ion concentration in arterial blood
PHPT	pulmonary hypertension
pHv	the negative logarithm of the hydrogen ion concentration in venous blood
PiO_2	partial pressure of inspired oxygen
PPE	post pneumonectomy pulmonary edema
ppm	parts per million
PsO_2	partial pressure of oxygen at the sensor for hypoxic pulmonary vasoconstriction
$P_{STARLING}$	pressure tending to collapse the starling resistor
Pv	pulmonary venous pressure
PVA	pressure-volume area
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance normalised for body surface area
Qs/Qt	shunt as a fraction of cardiac output
Qt	cardiac output
R	resistance
RA	right atrium
Rc	the resistor representing characteristic impedance: as this is not frequency dependent, it is represented by a simple resistor in the Windkessel model of the circulation.
Rc	characteristic impedance
RCA	right coronary artery
R_o	characteristic impedance
Rp	peripheral resistance
RQ	respiratory quotient
RV	right ventricle, or right ventricular
RV	residual volume
RVEDP	right ventricular end-diastolic pressure
RVEDV	right ventricular end-diastolic volume
RVEDVI	right ventricular end-diastolic volume index
RVEF	right ventricular ejection fraction

RVH	right ventricular hypertrophy
RVSW	right ventricular stroke work
RVSWI	right ventricular stroke work index
S□O_2	mixed venous oxygen saturation
S1, S2, S3 …	step one, step two, step 3 etc
SaO_2	arterial oxygen saturation
SAP	systolic arterial pressure (systemic)
ScO_2	saturation of hemoglobin of pulmonary capillary blood
SD.	standard deviation
secs	seconds
SI	stroke index ($ml.m^{-2}$)
SIRS	systemic inflammatory response syndrome
SNS	sympathetic nervous system
SPAP	systolic pulmonary artery pressure
SV	stroke volume
SVR	systemic vascular resistance
SW	stroke work
td	duration of diastole
TLC	total lung capacity
ts	duration of systole
ug	microgram
V/Q	ventilation-perfusion…
VC	vital capacity
VC	vital capacity
Vd	dead volume of the ventricle; similar to the unstressed volume of the ventricle
V_E	expired minute volume
Ved	end diastolic volume of the ventricle
VI	inspired minute volume
Vo	volume of the ventricle when the intra-cavitary pressure is zero
VO_2	oxygen consumption per unit time
VO_2I	oxygen consumption per unit time indexed for body surface area
VO_2max	maximal consumption of oxygen
vs.	versus
Vt	tidal volume
Zc	characteristic impedance
ZEEP	zero end expiratory pressure
Zin(ω)	input impedance at frequency ω

5.2 Information and consent document used in current study

A study of right ventricular function during one lung anesthesia

Patient information and consent document

A BACKGROUND TO THE STUDY/INFORMATION

1. This clinical study has been approved by the Ethical Committee of the University of Stellenbosch.
2. One lung anesthesia is a standard and normal part of intrathoracic surgery that is well tolerated. It is essential to use it during your surgery. The aim of the study is to observe the function of the right side of the heart (which pumps blood through the lungs) during one lung anesthesia. In addition, the effect of right ventricular function on the effectiveness of the circulation as a whole will be studied. The influence of low dosage of dobutamine and/or nitric oxide will be studied.

   The use of dobutamine and/or nitric oxide[#] may in fact benefit the function of the right ventricle and improve circulation and oxygenation as a whole during one lung anesthesia. The data so gathered would be used to further the understanding of heart function during one lung anesthesia. A total of 30 to 60 patients over a period of 2 years will be studied.
3. The intraoperative conduct of this project is similar to the standard anesthetic protocol and risk for one lung anesthesia and compared to the normal clinical practice of one lung anesthesia.
4. All personal information will be treated as highly confidential, but the data gathered will be used in a doctoral thesis or publication.
5. If any of the information gathered should be pertinent to your health, you will be informed accordingly.
6. We wish to make it clear that your participation in this study is voluntary and that should you refuse to take part, your decision will not place you at a disadvantage in any way. Your participation in this study may also be discontinued without your consent by the Investigator if the Investigator feels that it is in your best interest. You may withdraw your consent at any time prior to surgery without prejudice to your future treatment.
7. You will not be subjected to clinically unproven or risky manoeuvres.

[#] Albeit that it was intended that patients were to be exposed to nitric oxideduring OLA, all the investigators attepts over a period of 2 years to obtain nitric oxide met with no success. No patient was thus ever exposed to nitric oxide.

B CONSENT

Patient Name: .....

Hospital Number: .....

I, the abovementioned confirm that I understand the information that is contained in this document and voluntarily agree to

1. Participation in the research project with the title: A study of right ventricular function during one lung anesthesia. The information and procedures have been satisfactory explained to me by Dr. ....., and
2. The administration of general anesthesia, and epidural analgesia, and
3. The use of nitric oxide and/or dobutamine which is well established therapy for the treatment of pulmonary hypertension, and
4. The use of devices (that are commonly used in the hospital during lung surgery) for monitoring of the circulation.

Signed at Tygerberg on .....

.....

Patient signature or right thumbprint

.....

Witness

IMPORTANT INFORMATION

Dear patient. Many thanks for your participation in the study. If at any time during the project you require further information about the project, please contact Dr. Levin at 938-9231

C DECLARATION BY/FOR THE RESEARCHER

I, ..., declare that I:

1. Explained the information contained in this document to the patient; and
2. He/she was given an opportunity to ask questions should anything not be clearly understood.

Signed Tygerberg on .....

.....

Researcher or Researcher's representative

.....

Witness

D DECLARATION BY TRANSLATOR

I, ... confirm that I

1. Have translated this document from English/Afrikaans to the patient, as well as the questions put by the patient to the researcher and subsequently translated this person's answers.
2. That the information so exchanged was a factually accurate version of what was actually explained to me.

Signed at Tygerberg on .....

.....

Signature of Translator

.....

Signature of Witness

5.3 World Medical Association Declaration of Helsinki[#]

5.3.1 Ethical principles for medical research involving human subjects

5.3.1.1 Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

[#] The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

5.3.1.2 Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the

subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case, the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

5.3.1.3 Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. *The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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* Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki.

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

1. Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
2. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

5.4 Complex numbers (including discussion of imaginary numbers and the modulus of a complex number)[#]

5.4.1 History: Quadratic and cubic equations or "Are real numbers not sufficient?"

The earliest fleeting reference to square roots of negative numbers occurred in the 1st century of the common era, in the work of the Greek mathematician and inventor, Heron of Alexandria, when he considered the volume of an impossible frustum[#] of a pyramid. During the mathematical reawakening in Western Europe in the 13th century, works in mathematics were translated from the Arabic into Latin allowing Western European scholars to learn about the medieval Arabic-language mathematics and the older Greek mathematics, such as "Euclid's Elements". In all this mathematics, only positive numbers were considered numbers. Negative numbers were not yet accepted as entities. (Some ancient cultures, including that of China and India, accepted negative numbers, but not yet, imaginary numbers). Negative numbers became more prominent when, in the 16th century, Italian mathematicians, Tartaglia and Cardano, discovered unsolvable formulae for the roots of third and fourth degree polynomial equations. However, no one likes a result that states, "the solution is impossible" (Batschelet, 1975). It was soon realized that these formulae, even if one was only interested in real solutions, sometimes required the manipulation of square roots of negative numbers. This was unsettling since negative numbers were not considered to be on firm ground at the time. Descartes (1596–1650) also studied the solution to polynomial equations. He called negative solutions "false" and treated other solutions (that is, complex numbers) as "imaginary". Descartes used the term "imaginary" in a derogatory sense. The existence of complex numbers was not completely accepted until Caspar Wessel described the geometrical interpretation thereof in 1799. This definition was rediscovered several years later and popularized by Carl Friedrich Gauss. The formal and correct definition, using pairs of real numbers, was eventually given in the 19th century.

[#] The information on complex numbers was adapted from the following sources:

1. Batschelet E. "Introduction to mathematics for life sciences". Second edition, 1975. Springer-Verlag, Berlin, Heidelberg, New York.

2. Claeys J. "An introduction to complex numbers". These webpages are located at http://home.scarlet.be/math Copyright 1997. Contact address of author is Johan.Claeys@ping.be

3. Joyce DE. "Dave's Short Course on complex numbers". Department of Mathematics and Computer Science. Clark University, Worcester, Massachusetts. These pages are located at http://www.clarku.edu/~djoyce/complex/

4. Wikipedia, the free encyclopedia. These pages are located at http://www.wikipedia.org

[#] *Frustum* is defined as a slice of a solid body (Chambers Maxi Dictionary, W and R Chambers, 1992)

5.4.2 Definition of a complex number

From the time that Gauss proved the Fundamental Theorem of Algebra, it was known that all complex numbers are constructed as an ordered pair of real numbers, each real number[Ψ] being associated with a second real number. A complex number (x,y) is written in the form:

$$x + yi \qquad \ldots\ldots\ldots\ldots\ldots\ldots \qquad \text{Equation 5.4.2.1}$$

Where the '+' and the i are just symbols for now, and x and y are real numbers. We call 'x' the real part and 'yi' the imaginary part of the complex number.

For example:

(2, 4.6) can also be written as 2 + 4.6i,

(0, 5) can also be written as 0 + 5i and,

(-5, 36/7) can also be written as -5 + (36/7)i

Note that

Instead of 0 + yi, we write 5i,

Instead of x + 0i, we write x and,

Instead of 0 + 1i, we write i.

C denotes the standard symbol for the set of all complex numbers. If the real number *x* is associated with an imaginary number (*x*, yi), R becomes a subset of C.

5.4.3 Geometric representation of a complex number

To provide complex numbers of the form x + yi with some kind of "reality", these numbers can also be displayed as a point or a vector on the two dimensional *xy*-plane (also referred to as the Gaussian or *complex* plane C) (Figure 5.4.1). This provides a second way to approach complex numbers, the first way being algebraically as in the expression x + yi.

The Gaussian or complex plane is constructed by drawing a horizontal x-axis indicating real numbers. This plane corresponds to the x-axis in a conventional *xy-coordinate* system. Then another vertical axis is drawn through the point representing the number zero. The vertical axis has the same unit of length as the horizontal axis. When the *xy*-plane is used as a representation of the complex plane, the *x*-axis is called by the name "*real axis",* and the *y*-axis is called the "*imaginary axis".* Using this graphical representation, it can also be appreciated that *real numbers* are to be considered as special cases (subsets) of complex numbers; *real numbers* are just the numbers *x + yi* when *y* is 0. For instance, the real number *2* is *2 + 0i.* On the other hand, imaginary numbers are a special case too, namely the numbers when x is zero i.e. 0 + yi.

The complex number x + yi can be simply represented on the Gaussian or complex plane by vector P or OP with coordinates (x,y) (Figure 5.4.1). Complex numbers are also sometimes referred to by a single symbol, for example z = x + yi.

[Ψ] *Real numbers* are all those numbers that are positive, negative, or zero. The symbol for real numbers is "R".

The addition of two complex numbers is just the vector addition of two vectors, and the multiplication with a fixed complex number can be seen as a simultaneous rotation and stretching (see Figure 5.4.3).

5.4.4 Modulus of a complex number

The modulus or absolute value of x + yi is defined as the square root of $(x^2 + y^2)$. This modulus of x + yi is written as |x + yi|. Furthermore, if P is the representation of x + yi in the Gauss-plane, the distance from the origin O to P is the modulus of x + yi. For example, |3 + 4i| = 5 (Figure 5.4.2).

5.4.5 Polar co-ordinates of complex numbers

It is convenient and useful to introduce polar co-ordinates for complex numbers. The distance from the origin to P is represented by r, and α is the angle between the positive x-axis and the line OP measured in a counterclockwise direction. Let x and y be the rectangular co-ordinates of P (Figure 5.4.2). Then

$x = r\cos\alpha$ ..... Equation 5.4.5.1 and

$y = r\sin\alpha$ ..... Equation 5.4.5.2

We may rewrite z = x + iy using Equation 5.4.5.1 and Equation 5.4.5.2 as

$z = r(\cos\alpha + i\sin\alpha)$ ..... Equation 5.4.5.3

Note that $r(\cos\alpha + i\sin\alpha)$ is called the polar representation of a+bi.

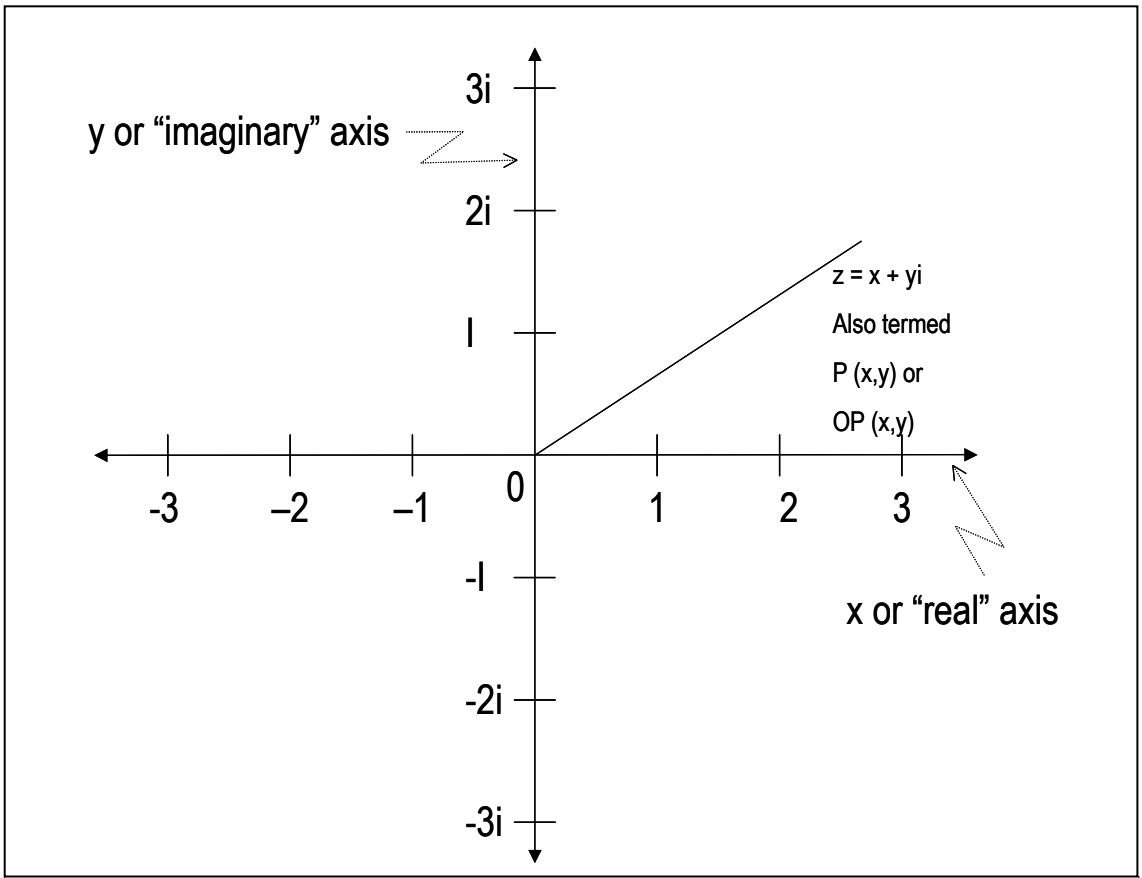

Figure 5.4.1. The geometric representation of a complex number in the Gaussian or complex plane. See text for details.

Note also that the polar angle α, is also called the argument or phase angle of a + bi. It can be represented in degrees or a number that is the angle represented in radians.

5.4.6 Addition and subtraction of complex numbers

The operations of addition and subtraction are now easily understood. To add or subtract two complex numbers, just add or subtract the corresponding real and imaginary parts. Therefore, if

$z_1 = x_1 + iy_1$ and $z_2 = x_2 + iy_2$ represent two imaginary numbers,

Then

$z_1 + z_2 = (x_1 + x_2) + i(y_1 + y_2)$ ..... Equation 5.4.6.1

$z_1 - z_2 = (x_1 - x_2) + i(y_1 - y_2)$ ..... Equation 5.4.6.2

For instance, the sum of 5 + 3*i* and 4 + 2*i* is 9 + 5*i*. For another, the sum of 3 + *i* and –1 + 2*i* is 2 + 3*i*.

As mentioned above, the addition of two complex numbers is just the algebraeic addition of two vectors (Figure 5.4.3). "Addition" can therefore be represented graphically on the complex plane C. Take the last example. The complex number $x_1,y_1 = 3 + i$ is located 3 units to the right of the imaginary axis and 1 unit above the real axis, while $x_2,y_2 = -1 + 2i$ is located 1 unit left and 2 units up. So the sum $(x_1,y_1) + (x_2,y_2) = 2 + 3i$ is 2 units right and 3 units up. So $z_1 + z_2$ is the vector corresponding with the sum of the two complex numbers. The addition of complex numbers corresponds with the addition of the corresponding vectors in the Gaussian-plane.

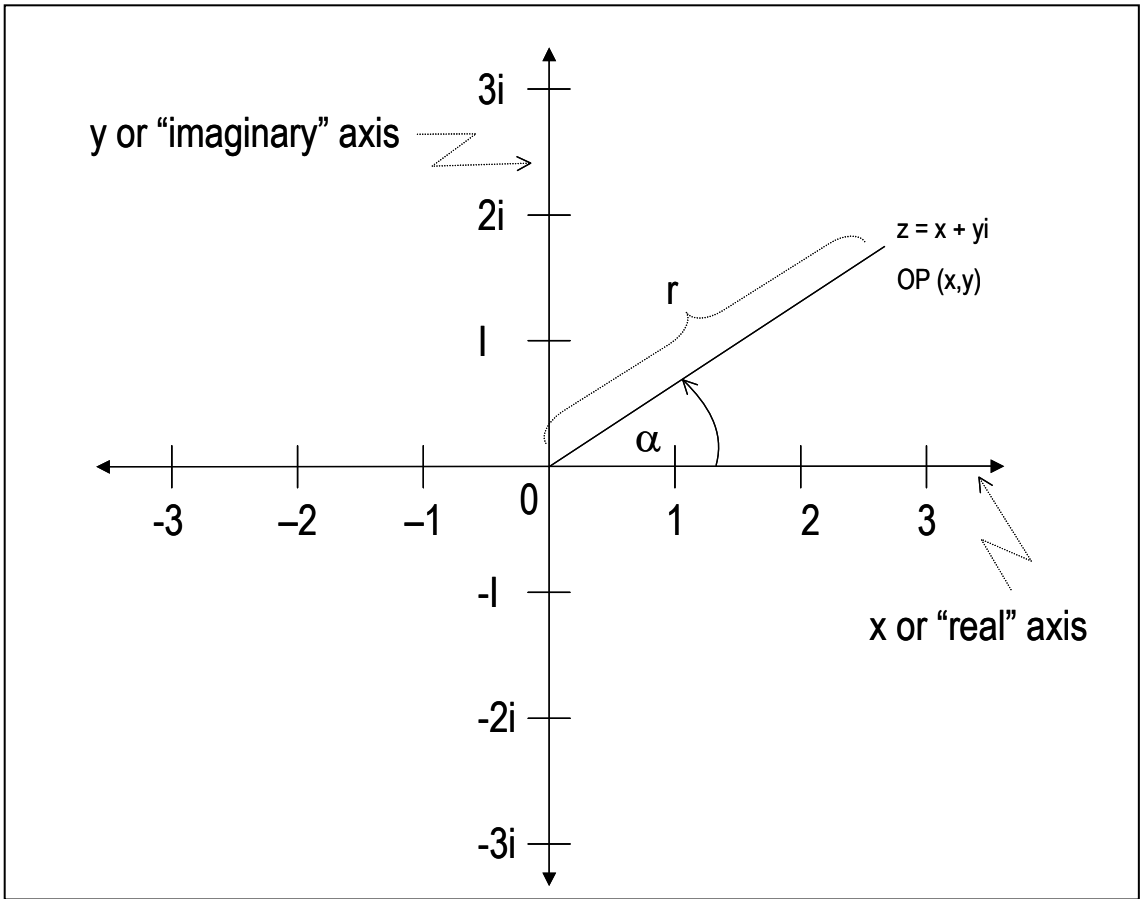

Figure 5.4.2. The modulus of a complex number, z = x + yi is represented as the distance from the origin O, to the point P.

5.4.7 Multiplication of complex numbers

To define multiplication, two steps are needed. First, the imaginary number i is managed as if it were a real number. For example,

$$(3 + 2i)(4 - 5i) = 12 - 15i + 8i - 10i^2 \quad \ldots\ldots\ldots\ldots \quad \text{Equation 5.4.7.1}$$

Secondly, if $i^2 = -1$, we can simplify Equation 5.4.7.1 to

$$(3 + 2i)(4 - 5i) = 12 - 15i + 8i - 10(-1) = (22 - 7i)$$

Therefore, if

$z_1 = x_1 + iy_1$ and $z_2 = x_2 + iy_2$ represent two imaginary numbers,

Then

$$z_1 z_2 = (x_1 + iy_1)(x_2 + iy_2)$$

$$z_1 z_2 = (x_1x_2 - y_1y_2) + i(x_1y_1 + x_2y_2) \quad \ldots\ldots\ldots\ldots \quad \text{Equation 5.4.7.2}$$

Multiplication with *i* corresponds to a counter clockwise rotation by 90 degrees (see Figure 5.4.4). The geometric content of the equation $i^2 = -1$ is that a sequence of two 90 degree rotations results in a 180 degree rotation. Even the fact (-1)(-1) = +1 from arithmetic can be understood geometrically as the combination of two 180 degree turns.

5.4.8 Applications of complex numbers

Complex numbers are used in signal analysis and other fields as a convenient description for periodically varying

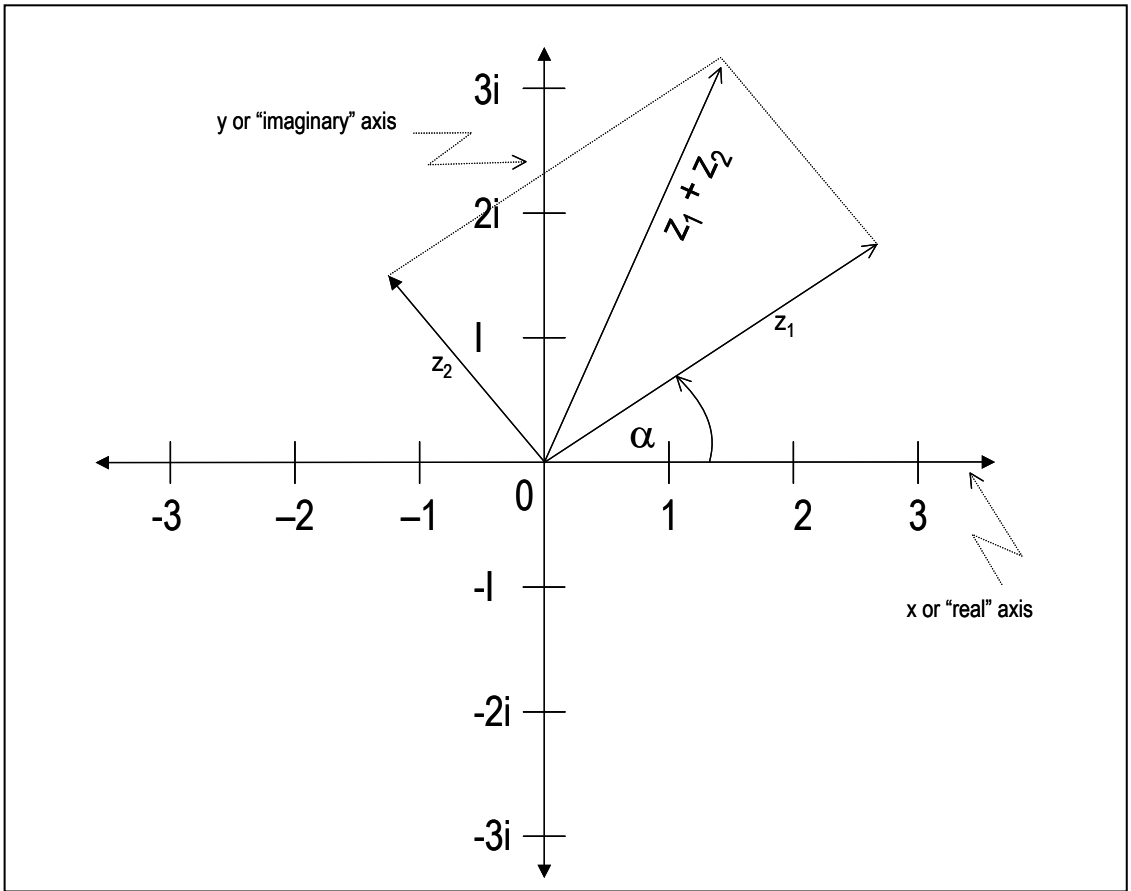

Figure 5.4.3. The addition of two complex numbers can be represented simply by vector addition.

signals. The absolute value $|z|$ is interpreted as the amplitude and the argument $\arg(z)$ as the phase of a sine wave of given frequency. If Fourier analysis is employed to write a given real-valued signal as a sum of periodic functions, these periodic functions are often written as the real part of complex valued functions of the form

$$f(t) = z\, e^{i\omega t} \qquad \ldots\ldots\ldots\ldots\ldots\ldots \qquad \text{Equation 5.4.8.1}$$

Where ω represents the angular frequency and the complex number z encodes the phase and amplitude as explained above. In electrical engineering, this is done for varying voltages and currents. The treatment of resistors, capacitors and inductors can then be unified by introducing imaginary frequency-dependent resistances for the latter two and combining all three in a single complex number called the impedance. (Electrical engineers and some physicists use the letter *j* for the imaginary unit since *i* is typically reserved for varying currents.)

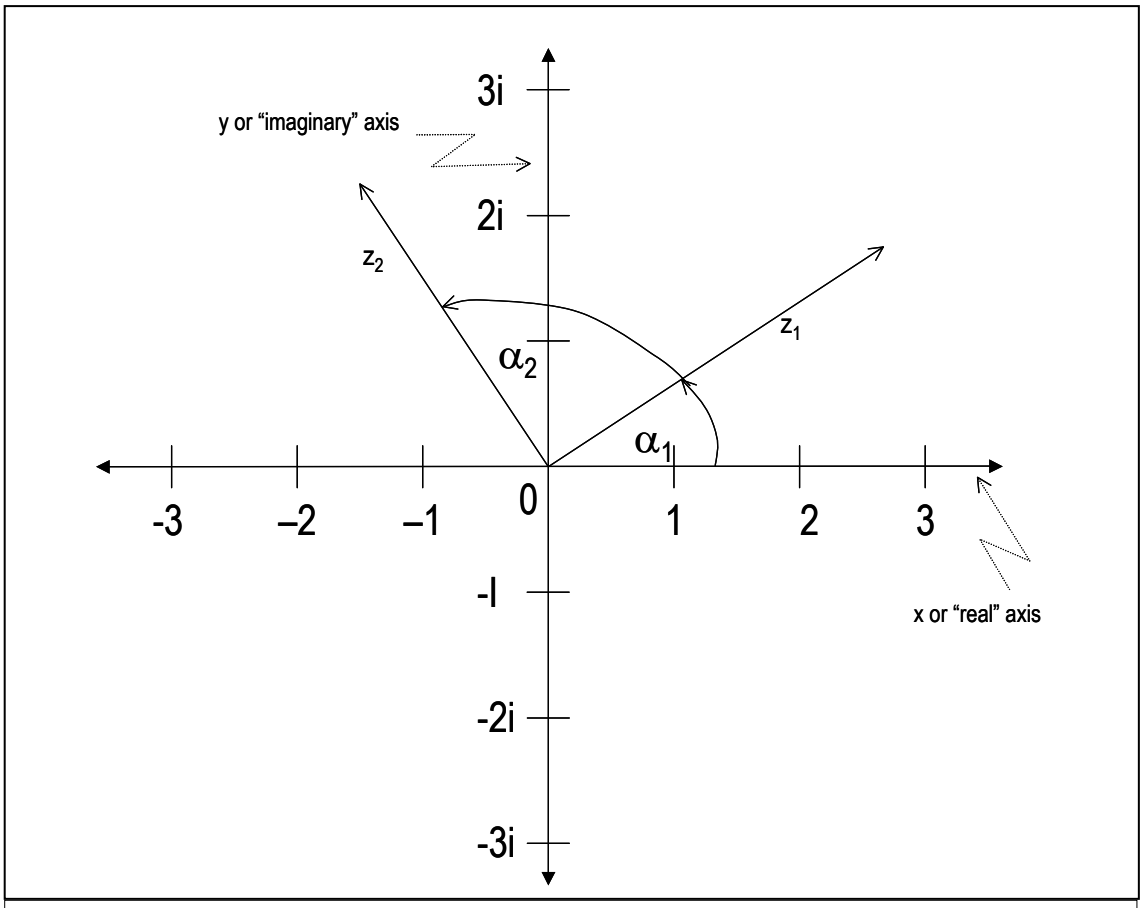

Figure 5.4.4. The multiplication of a complex number by i results in its counter clockwise rotation by 90^{o}.

5.4.9 Proof that area under the diastolic curve, Ad = Po.τ(1 – e $^{-td/\tau}$)

In Sunagawa, Maughan et al. 1988, it is assumed that the area under the diastolic curve, Ad = Po.τ(1 – e $^{-td/\tau}$). The following is proof thereof.

$$Ad = \int_0^{td} Po\, e^{-td/\tau} dt$$

$$= Po \int_0^{td} e^{-td/\tau} dt$$

$$= -\tau.Ps \int e^{-td/\tau} dt$$

$$= -\tau.Ps.\ e^{-td/\tau} dt \Big|_0^{td}$$

$$= -\tau.Ps.\ (e^{-td/\tau} - e^{-0/\tau})$$

$$= -\tau.Ps.\ (e^{-td/\tau} - 1)$$

$$= \tau.Ps.\ (1 - e^{-td/\tau})$$

This proof is attributed to Pieter de Kock, Faculty of Electrical and Electronic Engineering, University of Strellenbosch.

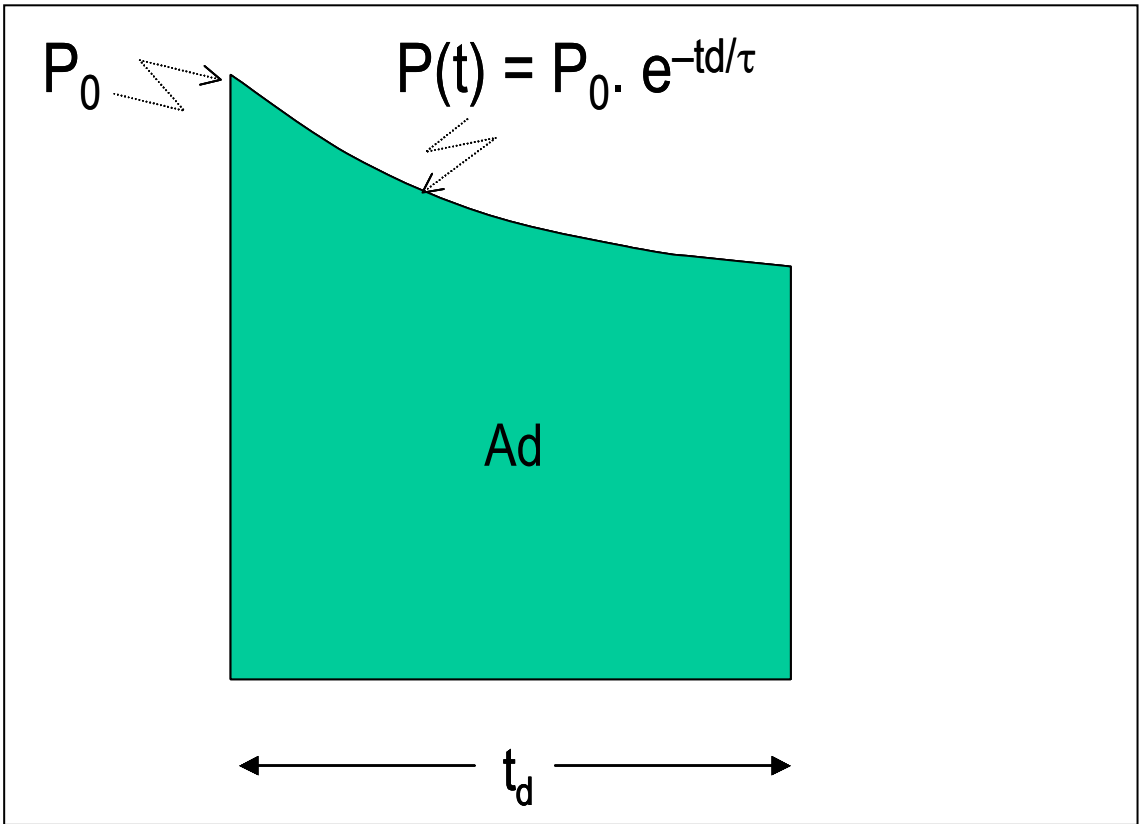

Figure 5.5.1. The area under the diastolic portion of the pulmonary or systemic arterial curve is depicted. It is assumed that the decline in pressure in diastole follows a mono-exponential curve. "τ" is the time-constant. The area under the curve is given by Po.τ(1 – e $^{-td/\tau}$).

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[Ψ] References were organized using Reference Manager for Windows, version 8.5. Wherever possible, references were imported from Medline directly into Reference Manager to ensure accuracy.

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