Comparison of minimally and more invasive methods of determining mixed venous oxygenation

Investigator

Dr Marli Smit

MB ChB (Stell) FCA (SA)

For fulfilment of the degree M Med (Anes)

Faculty of Health Sciences, University of Stellenbosch

Co-investigator and co-promoter

Prof Andrew I Levin

MB ChB, DA (SA), MMed (Anes), FCA (SA), PhD.

Statistician

Prof JF Coetzee

BSc, MBChB, MMed (Anes), FCA (SA) DipDat (UNISA), Bsc, PhD.

Declaration

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

Protocol Abstract

Circulatory efficiency is the relationship between oxygen consumption and global oxygen delivery.[1]Manipulation of circulatory efficiency has been shown to be beneficial in critically ill surgical and medical adults, and in children.[2] Circulatory efficiency is best assessed by measuring an index of mixed venous oxygenation (content, saturation and partial pressure) and viewing this in the context of oxygen consumption.[3] Mixed venous oxygenation has until now required intermittent sampling via a pulmonary artery catheter, or by using a pulmonary artery catheter equipped with a fibre optic bundle for continuous mixed venous oxygen saturation monitoring.[4] However, the use of the pulmonary artery catheter is declining as it has been (correctly or incorrectly) indicted of being an "invasive" tool.[5]

Attempts have been made to estimate mixed venous oxygenation non-invasively using the "NICO" monitor[6], near infrared spectroscopy[7], skeletal muscle oxygen saturation[8], thenar muscle oxygen saturation[9] and transtracheal pulse oximetry.[4]While all of them effectively trended mixed venous oxygen saturation, their accuracy and use as a resuscitation endpoint are in doubt. Sampling central venous as a surrogate of mixed venous oxygenation is fraught with problems, particularly in sicker patients. Significant differences in oxygenation can be demonstrated between the pulmonary arterial and central venous sampling sites in shock states,[3, 10] in acutely ill post-surgical patients [11] and under varying hemodynamic conditions.[12]

With the decline in the use of the pulmonary artery catheter, minimally invasive cardiac output determination is becoming increasingly popular. Apart from that their accuracy (particularly un-calibrated devices) has been questioned; they also cannot determine mixed venous oxygen saturation.

To obtain a more reliable and refined, but less invasive, estimate of mixed

venous oxygenation would be beneficial. The primary aim of this study was therefore to investigate whether venous oxygenation (mixed venous oxygen content, saturation and partial pressure) could be accurately predicted by minimally invasive methods of determining cardiac output and non-invasive calorimetric methods of measuring oxygen consumption. The methods compared were the current invasive gold standard represented by direct sampling of mixed venous blood and thermodilution cardiac output using a pulmonary artery catheter, with a less invasive method of calculating mixed venous saturation, the latter comprised of 4 elements:

1. Cardiac output was measured using a minimally invasive technique, namely lithium dilution (LiDCo®).
2. Oxygen consumption was measured with a non-invasive calorimetric device (M-COVX™ module manufactured by General Electric Corporation).
3. Arterial oxygen content was estimated using blood sampled via an arterial catheter.
4. These 3 variables were inputted into Fick's equation and solved for venous oxygen content ($CvO_2 = CaO_2 – VO_2/CO$). Thereafter, using the calculated venous oxygen content as well as the haemoglobin concentration, mixed venous oxygen saturation and partial pressure was estimated using an Excel® spreadsheet (Appendix G) relating oxygen saturation and partial pressure using standard oxygen dissociation curve formula, and calculating oxygen content from various haemoglobin concentrations.

Analysis of the data was performed predominantly using Bland Altman analysis. LiDCo® derived cardiac output overestimated that measured using intermittent thermodilution PAC by a clinically significant average of 0.82liters/minute or 26%. The pulmonary artery catheter derived oxygen consumption underestimated that measured by the metabolic module by 52 ml/minute or 27%. Oxygen consumption was the parameter having the largest percentage error (27%) and difference between the Bland Altman upper and lower limits of agreement. The difference between oxygen

consumption measured by indirect calorimetry is expected to exceed that calculated using the indirect Fick method by 20 to 30% because intra-pulmonary oxygen consumption is excluded when using this method.[13] However, the scatter exhibited by the calorimetry estimations of oxygen consumption was probably the major reason for the discrepancy between the calculated and measured mixed venous oxygenation variables.

Despite small (12.0 to 26.3 %) differences between measurements in individual patients, venous oxygenation variables measured by the invasive and less invasive techniques were statistically different. We also considered the magnitude of these differences to be clinically significant as we were of the opinion that relying on the calculated results could adversely impact clinical decision-making.

In conclusion, we could not estimate venous oxygenation accurately enough using minimally invasive methods of determining cardiac output and non-invasive methods of measuring oxygen consumption to be clinically useful.

Protokol Opsomming

Sirkulatoriese effektiwiteit is die verhouding tussen suurstof verbruik en globale suurstof lewering.(1) Manupilasie van sirkulatoriese effektiwiteit is voordelig in kritiese siek chirurgiese en mediese volwassenes, asook in kinders.[2] Sirkulatoriese effektiwiteit word akkuraat bepaal deur gemengde veneuse suurstof (inhoud, saturasie en parsiële druk) te beskou in die lig van suurstof verbruik.(2) Gemengde veneuse saturasie bepaling het tot onlangs afgehang van die neem van intermitterende bloedmonsters via 'n pulmonale arterie kateter: die alternatief is deurlopende gemengde veneuse saturasie monitering met 'n veselopties toegeruste pulmonale arterie kateter.(3) Die gebruik van die pulmonale arterie kateter is egter aan die afneem aangesien dit (reg of verkeerd) as 'n baie indringende moniterings apparaat beskou word.[5]

Pogings is al aangewend om gemeng veneuse saturasie te bepaal op 'n nie-indringende manier. Onlangse studies het voorgestel dat gemengde veneuse saturasie afgelei kan word deur die gebruik van die "NICO" monitor(4), naby infrarooi spektroskopie(5), skeletspier suurstof saturasie(6), tenarespier suustof saturasie(7) en transtrageale polsoksimetrie(3). Die meerderheid van bogenoemde was akkuraat genoeg om die tendens van die verskille in gemengde veneuse saturasie te volg. Die akkuraatheid van genoemde tegnologieë as betroubare weergawes van gemengde veneuse saturasie en hulle gebruik as eindpunt tydens resussitasie word egter in twyfel getrek. Sentraal veneuse saturasie kan ook nie as surrogaat vir gemeng veneuse saturasie gebruik word nie, veral nie in siek pasiënte nie. Groot verskille in oksigenasie bestaan tussen gemengde- en sentrale veneuse saturasie in pasiënte wat geskok is (2;8), in akuut siek postoperatiewe pasiënte(9) en in hemodinamies onstabiele toestande.(10)

Minimaal indringende kardiale omset bepaling raak al hoe meer gewild soos

die gebruik van die pulmonale arterie kateter afneem. Behalwe dat hierdie toerusting (veral die ongekalibreerde toestelle) se akkuraatheid al bevraagteken is, kan hulle ook nie gemengde veneuse saturasie bepaal nie.

Dit sal dus voordelig wees om ‘n betroubare, akkurate en minimaal indringende metode te identifiseer om gemengde veneuse saturasie te bepaal. Die primêre doel van hierdie studie was om te bepaal of sirkulatoriese effektiwiteit (gemengd veneuse suurstof inhoud, saturasie en parsiële druk) akkuraat voorspel kan word met behulp van minimaal indringende metodes van kardiale omset bepaling en nie-indringende kalorimetriese metodes van suurstof verbruik. Die goue standard verteenwoordig deur ‘n direkte gemeng veneuse bloed monster en termoverdunning kardiale omset, gemeet met behulp van die pulmonale arterie kateter, is dan vergelyk met ‘n minder indringende metode. Tydens die minder indringende metode is gemengde veneuse saturasie as volg bereken is:

1. Kardiale omset is gemeet deur middel van litium verdunning (LiDCo®), ‘n minimal indringende tegniek.
2. Suurstof verbruik is gemeet deur ‘n non-indringende kalorimetriese toestel (M-COVX™ module vervaardig deur “General Electric Corporation”).
3. Arterieële suurstof inhoud is bereken met behulp van bloed verkry vanaf ‘n arteriële kannule.
4. Hierdie drie veranderlikes tesame met Fick se vergelyking is toe gebruik om veneuse suurstof inhoud te bereken ($CvO_2 = CaO_2 – VO_2/CO$). Deur gebruik te maak van die hemoglobien konsentrasie en veneuse suurstof inhoud, is gemeng veneuse suurstof saturasie en parsiële druk daarna bepaal in ‘n “Excel®”sigblad (Bylae G) wat die standaard formule vir die suurstof dissosiasie kurwe gebruik het.

Analise van die data is hoofsaaklik uitgevoer deur gebruik te maak van die Bland Altman analise. LiDCo® afgeleide kardiale omset het dié gemeet deur intermitterende termoverdunning deur die pulmonale arterie kateter oorskat

deur ‘n klinies relevante gemiddeld van 0.82liter/minuut of 26%. Die pulmonaal arterie kateter afgeleide suurstof verbruik het dié gemeet deur die metaboliese module onderskat met 52ml/minuut of 27%. Suurstof verbruik was die parameter met die grootste persentasie fout (27%) en verskil tussen die Bland Altman boonste en onderste limiete van ooreenkoms. Ons het verwag dat indirek kalorimetriese gemete suurstof verbruik 20 – 30% meer sou wees as suurstof verbruik bereken deur die indirekte Fick metode. Die rede hiervoor is dat intra-pulmonale suurstof verbruik 20 - 32% van heel liggaam suurstof verbruik bydra, en Fick-VO2 sluit hierdie intra-pulmonale suurstof verbruik uit. Die verspreiding soos aangetoon deur die kalorimetriese bepalings van suurstof verbruik was moontlik die hoofrede vir die onvereenigbaarheid tussen die berekende en gemete gemeng veneuse oksigenasie veranderlikes.

Ongeag die klein (12 tot 26.3%) verskille tussen metings in individuele pasiënte, is die veneuse oksigenasie veranderlikes gemeet deur die indringende en minder indringende tegnieke statisties verskillend. Ons is ook van mening dat die grootte van die verskille klinies belangrik is, aangesien besluite geneem op grond van die berekende gemeng veneuse saturasie kliniese besluitneming negatief mag beïnvloed.

In samevatting, kan ons nie veneuse oksigenasie akkuraat genoeg bepaal, met behulp van minimaal indringende metodes van kardiale omset en nie-invasiewe metodes van suurstof verbruik bepaling, om klinies van waarde te wees nie.

Acknowledgements

I would like to acknowledge Professor Andrew Levin for his initiative that led to the realization of this research study and thank him for his guidance and input throughout the project.

I would also like to thank Professor Johan Coetzee of the Department of Anaesthesiology and Critical Care, University of Stellenbosch for assisting with the statistical analysis.

Table of Contents

Equations and abbreviations used

Abbreviations:

CvO2	mixed venous oxygen content	ml O2/dl
VO2	oxygen consumption	ml/kg/min
DO2	oxygen delivery	ml/kg/min
SvO2	mixed venous oxygen saturation	%
PvO2	mixed venous oxygen partial pressure	kPa
CaO2	arterial oxygen content	ml O2/dl
ScvO2	central venous oxygen saturation	%
CO	cardiac output	l/min
PaO2	partial oxygen pressure	kPa

PAC	- pulmonary artery catheter
CV	- coefficient of variation
CE	- coefficient of error
TD	- thermodilution
PE	- percentage error
N	- number of units in a sample
SD	- standard deviation
CI	- confidence interval
ml/minute	- millilitre per minute
kPa	- kilopascal
ml O2/100ml blood	- millilitres oxygen per 100milliliters of blood
r	- correlation coefficient
r^2	- coefficient of determination
feO2	-expiratory oxygen fraction
fiO2	-inspiratory oxygen fraction
min	-minute
dl	-desi-litre
%	-percentage
kg	-kilogram

O2 -oxygen

Mixed venous oxygen content:

$CvO_2 = CaO_2 - VO_2/CO$ Equation 1

$CvO_2 = 1.39 \text{ X Hb X } SvO_2 + 0.003XPaO_2$ Equation 2

Arterial oxygen content:

CaO_2= [HbXSaturation/100X1,39]+ 0,003PaO_2 Equation 3

Oxygen consumption:

VO2 = CO(CaO2 – CvO2) Equation 4

Mixed venous saturation:

$SvO_2 = (CvO_2 - 0{,}003PaO_2)/ 1{,}39.Hb$ Equation 5

List of Figures

List of Tables

The tables describe the data as follows:

Literature review

Mixed venous oxygenation is determined by the relationship between oxygen consumption by and oxygen delivery to the tissue.[1] Mixed venous oxygenation, or more specifically mixed venous saturation (SvO2) and partial pressure of oxygen are the gold standard by which the global oxygen supply-demand relationship is assessed, the normal values approximating 75% and 5.3 kPa, respectively.[14] Mixed venous oxygen content is however a parameter that is more difficult for clinicians to interpret than mixed venous oxygen saturation. Mixed venous oxygen saturation, partial pressure of oxygen and content all decrease (if oxygen consumption is constant) in the presence of an inadequate global demand-supply- relationship.[15, 16]

Mixed venous oxygen saturation (SvO2) has been shown to be of great value as a diagnostic and prognostic tool in the treatment of patients. [15] SvO2 monitoring provide an early and accurate reflection of the effect of therapeutic interventions, and will therefore improve the management of patients by guiding therapy.[17] Advantages of continuous monitoring of mixed venous oxygen saturation, include the evidence of circulatory efficiency in situations where peripheral devices; for example pulse oximeter, arterial cannulae and ECG electrodes, become unreliable due to technical difficulties. It will also alert the clinician early to the development of potential problems, since a decrease in SvO2 in conjunction with normal oxygen consumption (VO2) is an early indicator of inadequate perfusion.

Continuous monitoring of mixed venous oxygen saturation is of specific value during vascular surgery involving the aorta. It has been demonstrated that each type of aortic reconstruction has its own SvO2 trend. The changes in SvO2 during these vascular operations will reflect the degree of underlying occlusive disease (extend of ischemia), and the extent of the collateral arterial circulation.[18]

SvO2 monitoring is also of value in the monitoring and management of ha emodynamic unstable medical patients(25), patients that have undergone cardiovascular procedures[19], those in cardiogenic shock[14] and in paediatric patients.[20] A high incidence of sudden SvO2 deteriorations predicts mortality during septic shock. It is therefore of prognostic value.[21]

SvO2 levels may be of economical value. It has been demonstrated that increasing oxygen delivery to achieve normal SvO2 values and lactate concentrations immediately after cardiac surgery, can decrease morbidity, shorten length of hospital stay, and thus reduce total costs.[19]

SvO2 play a role in the treatment of neonates. Mixed venous oxygen saturation may guide cardiovascular therapy, fluid and blood transfusion therapy, reveal left-to-right intra-cardiac shunting and critical levels of PaO_2 in order to reduce hypoxic and hyperoxic tissue injury.[22] When cardiac output and haemoglobin levels are adequate, inhaled oxygen should only be indicated if SvO2 < 50%. Lastly since a normal SvO2 (in the light of normal oxygen consumption) imply a normal oxygen supply-demand relationship[23], a normal SvO2 may offer some assurance, especially under challenging circumstances.

Mixed venous oxygenation is typically measured by intermittent sampling from the pulmonary artery catheter, or by a specially designed pulmonary artery catheter with a fiber-optic bundle for continuous mixed venous oxygen saturation monitoring.[4]

Currently, measurement of mixed venous oxygenation depends on the placement of a pulmonary artery catheter. Insertion of a pulmonary artery catheter is an invasive procedure and it would be ideal if circulatory efficiency could be determined by using less or minimally invasive methods. Furthermore, the clinical utility and benefits of monitoring mixed venous oxygenation less invasively could promote its use in critically ill patients.[24]

The risk of a major complication associated with pulmonary arterial catheterisation (PAC) is about 10%. It should be remembered that one of the alternatives to the PAC, central venous cannulation, entails many of the same risks as a PAC. Indeed, in a recent review, McGee and Gould concluded that more than 15% of patients who receive central venous catheters would develop some form of complication. They reported the risk of a mechanical complication occurring as 5 to 19%, an infectious complication as 5 to 26 percent, and a thrombotic complications as 2 to 26%.[25] In comparison to central venous pressure monitoring, the specific risks of the PAC are conduction block, pulmonary infarction and pulmonary artery rupture.[26, 27]

Currently, other attempts are being made to determine mixed venous oxygenation by using non-invasive methods. Recent studies suggested that SvO2 might be estimated using a NICO (non-invasive cardiac output) monitor [6], near infrared spectroscopy[7], skeletal muscle oxygen saturation[8], thenar oxygen saturation[9] and trans-tracheal pulse oximetry.[4] Of all these techniques, the most feasible non-invasive monitor estimating pulmonary artery oxygen saturation is trans-tracheal pulse oximetry.[4]

Mixed venous oxygenation values measured by the NICO monitor cannot be used interchangeably with those determined by the pulmonary artery catheter.[6]Regional cerebral oximetry via near infrared spectroscopy correlates well with SvO2 trends obtained via pulmonary artery catheter, but cannot be used to predict absolute values of SvO2.[7] Skeletal muscle oxygenation and thenar oxygenation also do not accurately reflect SvO2 in patients with left heart failure complicated by severe sepsis or septic shock.[8, 9]Therefore, while the majority of the aforementioned techniques may show a trend in mixed venous oxygen saturation, their use in defining the endpoint of resuscitation may be misleading. More refinement is required to obtain a more reliable estimate of mixed venous oxygen saturation less invasively.

Sampling central venous gases (ScvO2) as a surrogate of mixed venous oxygenation is fraught with problems, particularly in the sickest patients. Large differences in oxygenation can be demonstrated between the pulmonary arterial and central venous sampling sites in shock states[3, 10], in acutely ill postoperative patients SvO2[11] and under varying ha emodynamic conditions.[12] Exact numerical values of mixed venous oxygen saturation are not equivalent to those of central venous oxygen saturation under varying haemodynamic conditions.[12] Several studies indicated that ScvO2 levels are consistently greater than those of SvO2 in shock.[28, 29] Therefore, central venous content or saturation may not be used instead of SvO2 in the management of patients in septic shock. [10]

The clinical usefulness of monitoring exact values of ScvO2 is thus strongly limited and reliance on Svo2 is still advised.

The rationale for development of a minimally invasive, accurate technique of determining mixed venous oxygenation is that such a technique must have an acceptable risk benefit ratio. These benefits could be utilized in the management of critically ill patients.[24]

The technique to be investigated

We compared the clinically acceptable invasive gold standard (pulmonary artery catheter, via which mixed venous blood can be directly sampled, cardiac output measured and oxygen consumption calculated using the arterio-venous oxygen difference) with a less-invasive method in which mixed venous oxygenation is calculated from other measured variables. M ixed venous oxygen content can be calculated (equation 1: $CvO_2 = CaO_2 – VO_2/CO$) using

1. Cardiac output measured via a minimally invasive technique, LiDCo®.
2. Non-invasive measurement of oxygen consumption with the metabolic monitor, M-COVX™.
3. Arterial oxygen content that can be measured in arterial blood samples.

Mixed venous oxygen saturation and partial pressure can be derived from mixed venous oxygen content (Equations 1 - 4) with the help of an Excel spreadsheet and lookup table provided haemoglobin concentration is known. [Appendix G]

Mixed venous oxygen content (CvO2) can be derived as follows:

$CvO2 = CaO2 – (VO2/CO)$ Equation 1

Where

- VO2 is whole body oxygen consumption in litres per minute
- CO is whole body cardiac output in litres per minute
- CaO2 is arterial oxygen content in millilitres oxygen per decilitre

Arterial oxygen content can be derived as follows:

$CaO2 = [Hb \times Saturation/100 \times 1,39] + 0,0031\ PaO_2(mmHg)$ Equation 3

Where

- 1,39 in ml/gHb

- Hb is haemoglobin in g/100ml
- PaO2 is the partial pressure of oxygen in mmHg

Oxygen consumption (VO2) can be calculated using the reverse Fick method:
$VO_2 = CO (CaO_2 – CvO_2)$ Equation 4

Oxygen consumption can also be measured non-invasively by indirect calorimetry in intubated patients.[30-32] When compared to the reverse Fick method, indirect calorimetry has demonstrated excellent accuracy and precision and allows continuous measurement of gas exchange.[33-35] The commercially available metabolic monitor, M-COVX™ (General Electric Datex Ohmeda) was utilised for this purpose as it can be easily incorporated into the existing anaesthetic monitoring systems.[33-36] [Appendix A]

A minimally invasive, reliable method of measuring cardiac output has recently been developed. The LiDCO™plus is a commercially available device.[37] Cardiac output is first accurately calculated using indicator (lithium) dilution. A known bolus dose of lithium is injected via a central or peripheral vein. A lithium sensitive sensor attached to an intra-arterial catheter measures blood lithium concentration. This enables accurate estimation of cardiac output. Using this as a calibration, pulse contour analysis of the intra-arterial wave form is then employed to estimate stroke volume and cardiac output continuously.[38-40] Using dye dilution or even thermodilution techniques to measure baseline cardiac output improves the accuracy of contour analysis determination of cardiac output. It is then suppose to be comparable to thermodilution over a wide range of cardiac outputs.[40-46] It has been suggested that the LiDCo® provides as, or even more reliable[47] estimates of cardiac output than thermodilution.[45-47] In cardiac and vascular anaesthesia, the placement of intra-arterial catheters is an essential, low risk procedure. Therefore, this method can be considered an accurate and minimally invasive technique of measuring cardiac output.

Hypotheses

The null hypotheses

a. There is an acceptable agreement between mixed venous oxygen calculated using minimally invasive techniques and measured from the pulmonary artery catheter.

b. The non-invasive (indirect) and reverse Fick methods of calculating oxygen consumption.

c. Less invasive and thermodilution methods of calculating cardiac output.

The alternative hypothesis

a. There is not an acceptable agreement between mixed venous oxygen calculated using minimally invasive techniques and measured from the pulmonary artery catheter.

b. The non-invasive (direct) and reverse Fick methods of calculating oxygen consumption do not produce similar results.

c. Less invasive and thermodilution methods of calculating cardiac output do not produce similar results.

Primary and secondary outcomes

The primary outcome of this study is to investigate whether circulatory efficiency (SvO2) can be accurately predicted /calculated by minimally invasive methods of determining cardiac output and non-invasive methods of measuring oxygen consumption.

Secondary outcomes include

1. Comparison of non-invasive (direct) and reverse Fick methods [equation 4] of calculating oxygen consumption
2. Comparison of minimally invasive (LiDCO™plus) and thermodilution methods of calculating cardiac output.

Method

This is a single centred, prospective, non-randomized, observational study done at Tygerberg Academic Hospital. The study population consisted of patients undergoing elective cardiac or vascular surgery.

The routine preparation for a patient undergoing cardiac or vascular surgery was followed. This included peripheral venous and arterial catheterisation and central venous (usually internal jugular vein) catheter insertion. Pulmonary artery catheters were inserted via a central venous sheath. These procedures were performed in the induction room under local anaesthesia and light sedation.

The anaesthetic technique was left to the discretion of the anaesthesiologist.

Inclusion criteria

The study included patients scheduled for cardiac or vascular surgery in which the attending anaesthesiologist was of the opinion (according to clinical criteria as set out by the American Heart Association Guidelines for the use of the pulmonary artery catheter) that the patient will benefit from insertion of a pulmonary artery catheter. Subjects scheduled for on or off-pump coronary artery bypass grafting, or valve replacement or repair, or vascular surgery involving the aorta were recruited.

Exclusion criteria

1. The primary exclusion criterion was patients in whom the anaesthesiologist did not plan to insert a pulmonary artery catheter.
2. Pregnant patients in the first trimester.
3. Patients with a respiratory rate of more than 35 breaths per minute or peak airway pressures exceeding 35 cm H_2O. [48]
4. A patient in whom thermodilution cardiac output may be inaccurate such as patients with severe tricuspid incompetence, pulmonary hypertension, or intra-cardiac shunts.

5. Patients in whom nitrous oxide was required.
6. Patients in whom an inspired oxygen fraction of more than 0.7 oxygen was required.[48]
7. Patients receiving lithium therapy.
8. Patients weighing less than 40 kilograms.
9. Aortic valve regurgitation [37]
10. Patients with an intra aortic balloon pump in situ.
11. Patients with highly damped peripheral arterial lines.
12. Patients with renal or liver failure.

The following measurements were performed. The data were noted on a sheet. (Appendix F).

1. Patient demographics; patient weight, height, sex and procedure.
2. Thermodilution cardiac output, using 10 millilitre boluses of normal sali ne. The cardiac output was determined in triplicate from which the average was taken.
3. Oxygen consumption was calculated using the reverse Fick method. The arterio-venous oxygen content difference was measured by sampling mixed venous and arterial blood which were analysed in a blood gas analyser. Haemoglobin concentration, haematocrit, oxygen partial pressure and saturation, carbon dioxide partial pressures, pH, temperature from the pulmonary artery catheter thermistor and inspired oxygen fraction were recorded.
4. Dye dilution calibration of the non-invasive cardiac output monitor was performed at least twenty minutes after administering the muscle relaxant , and again after known haemodynamic changes (e.g. after weaning from bypass and after un-clamping of the aorta.) Cardiac output was taken as the average cardiac output during the minute preceding the thermo dilution cardiac output measurement.
5. The lithium dose was administered by an intravenous injection into a central vein. A single dose of 0.075mmol (0.5ml), 0.15mmol (1ml) or 0.3mmol (2ml) lithium chloride is required per cardiac output

determination. The dose chosen was the smallest thatl produce an arterial plasma lithium dilution curve with a peak of between 0.2 and 0.8mM. Each dose was limited to a maximum of 0.3mmol (2ml) lithium chloride. We never used more than the cumulative allowable dose of lithium chloride, which is 3mmol (20ml of solution) for a single patient.

6. Non-invasive oxygen consumption was measured as the average oxygen consumption during the minute preceding the thermodilution cardiac output measurement. The M-COVX™ module was calibrated each week using 95% oxygen and 5% carbon dioxide mixture. The device was allowed to warm up for 5 minutes prior to use and the module sensor was placed between the Y-connector of the ventilator tubing and the tracheal tube.
7. Data were recorded from the General Electric Datex Ohmeda physiological monitor to a computer using "S5 Collect", a dedicated program designed for these purposes. Oxygen consumption was recorded and exported for subsequent analysis.
8. Vasopressor, vasodilator and inotropic support were noted as these could influence the accuracy of the measurements.

Data were collected at evenly spaced times as well as the same number of readings before and after bypass/ clamping and unclamping of the aorta.

We performed the following calculations:

1.Arterial oxygen content. [Equation3]

2.Venous oxygen content. [Equation 2]

3.Oxygen consumption [Equation 4], using the average or three thermodilution cardiac output measurements and the arterial and venous oxygen content.

Quality control measures:

1. **Thermodilution cardiac output:**

a. An inline temperature sensor was used
b. The cardiac output was determined from the average of three thermodilution estimates of cardiac output, each of which was within 10% of each other.

2. **Mixed venous blood sampling** from the right ventricle. Ten millilitre samples of blood were drawn for analysis. Before and after sampling, the location of the pulmonary artery catheter in the right ventricle was confirmed by inspection of the pressure waveform.
3. **Arterial blood gases.** Ten millilitre samples of blood were drawn for analysis. Blood was analysed immediately using the GEMRPremier 3000 (Model 5700) blood gas machine. (Automatic calibration of the blood gas machine was performed after each blood sample being analysed. A manual calibration as well as replacement of the cartridge was done by the theatre technologists after every 450 tests.)
4. **Non-invasive cardiac output.**
    a. The device was calibrated using standard injection of lithium as described by the manufacturer.
    b. The LiDCO™ system flow through cell assembly was flushed through with heparinised saline immediately after use until the blood has cleared from the cell.
    c. Some authors[49] propose that recalibration can be performed only every 24 hours. Nonetheless, we were concerned about significant potential for changes in impedance after bypass and unclamping of the aorta. Therefore, we calibrated the device after induction and again after any known hemodynamic changes.[41]
    d. No dose of muscle relaxant was given in the 20 minutes before calibration.
    e. The use of brachial arterial cannulation was preferred.
5. **Non-invasive oxygen consumption:**
    a. The device was calibrated weekly using 95% oxygen and 5% carbon dioxide mixture. The baseline check of the carbon dioxide sensor was made through a carbon dioxide absorber.

b. The device was allowed to warm up for 5 minutes before use as recommended by the manufacturers.
c. An original sensor was used to determine tidal and minute volumes.
d. No breathing system filter was used.
e. No heated water bath humidifier was used.
f. The breathing system pipes were emptied periodically from any water collected in the system.

6. The patients were haemodynamically stable, as determined by maintenance of blood pressure and the inotropic and vasoactive drug requirements at the time the measurements were made.
7. If intravenous fluid or blood is being rapidly administered, it was terminated one minute before measurements were recorded.

Statistical methods

This is a pilot study; therefore there are no data on which to base a power analysis for this study.

Our plan was to collect data from 10 patients over a 6 month period. If needed we would have used this data to determine the number of patients needed to expand the study. After collecting the initial data we decided not to expand on the study.
The reasons for that was that
- The amount of variables involved made the study practically challenging and the results inaccurate
- It was difficult to recruite patients, seeing that all of them needed a valid reason for PAC insertion
- The cost involved also needed to be justified. (PAC insertion as well as the Lithium used to calibrate the LiDCO involved R1800 per patient.)

The data collected were analyzed using bland-altman plots. Significance was primarily evaluated looking at whether the data expressed in the Bland Altman plots were clinically acceptable or not.

One patient is not one set of data, we took up to three readings from one patient. This is individual snap shots of data, and not to be seen as individual patients. A data snap shot consisted of a PAC cardiac output reading (the average of 3 readings), a VO2 reading averaged over one minute, LiDCO CO reading also average over the same minute and a arterial and mixed venous blood gas taken immediately after the readings were collected.

Ethical considerations

1. The technique described is minimally invasive.
2. There were minimum risks for the patient.
3. Blood samples comprised only 10 millilitres at a time.
4. Patients enrolled were those who were scheduled to have a pulmonary artery catheter inserted.
5. The population studied could be considered vulnerable, but we managed them ethically. Informed consent was obtained.
6. The study population consisted of patients undergoing elective cardiac and vascular surgery at Tygerberg Academic Hospital, and which required pulmonary artery catheter insertion.
7. Participants were not exposed to any additional risks.
8. We were of the opinion that this study is sound. Patient autonomy was respected through proper consent before enrolment. The study is observational and no new interventions were undertaken, it did not influence the patient's management in any way. The aim of this study is to supply doctors with a more accessible mixed venous oxygen saturation determination. This would imply more scientific patient care with less risk involved.
9. This research study was submitted to the Committee for Human Research at the University of Stellenbosch for approval and was done according to internationally accepted ethical standards and guidelines.
10. Informed consent was obtained from patients. (Appendix C)
11. A consecutive number was assigned to each patient and data capture and presentation were performed with these numbers. Patient privacy and confidentiality were protected.
12. Participants had the right to withdraw from the study at any time.

Data management

Intra operative data was collected on a predetermined data sheet. (See A ppendix F) The data were de-identified; data could therefore not be traced back to a specific individual.

The data was entered into a Microsoft Excel® spreadsheet for processing and statistical analysis.

Results

Presentation of results

Unless stated otherwise, data are presented as mean. For the sake of clarity, other statistics describing the distribution of the data are presented in the relevant tables and omitted in this section.

Tables

The tables describe the data as follows:

Table 1: Bland Altman plots

Table 2: Mountain plots.

Table 3: Descriptive statistics of the measured and calculated parameters.

Table4: Correlation coefficients

Table5: Accuracy/bias and precision.

Table 6: Patient demographics and problems encountered.

Figures

Figures 1 to 6 portray the Bland Altman plots for the different techniques of measuring the following parameters:

Figures 1A, 1B, 1C, 1D: Cardiac output;

Figure 2A and 2B: Oxygen consumption;

Figures 3A and 3B: Mixed venous oxygen content;

Figures 4A and 4B: Mixed venous oxygen saturation;

Figures 5A and 5B: Mixed venous oxygen partial pressure;

Figure 6A and 6B: Mixed venous oxygen partial pressure corrected for temperature and pH.

Figure 7: Cardiac output determined by the pulmonary artery catheter and LiDCO on the y and x-axes respectively.

Figure 8: Oxygen consumption determined by the pulmonary artery catheter and oxygen consumption module on the y and x-axes respectively.

Figure 9: Mixed venous oxygen content determined from pulmonary artery

catheter data and that calculated using minimally invasive techniques on the y and x-axes respectively.

Figure 10: Mixed venous oxygen saturation determined from pulmonary artery catheter data and that calculated using minimally invasive techniques and virtual oxygen dissociation curve on the y and x-axes respectively.

Figure 11: Mixed venous partial pressure determined from pulmonary artery catheter data and that calculated using minimally invasive techniques and virtual oxygen dissociation curve on the y and x-axes respectively.

Figure 12: **Mixed venous partial pressure corrected for temperature and pH** determined from pulmonary artery catheter data and those calculated using minimally invasive techniques and the oxygen dissociation curve on the y and x-axes respectively.

In the Bland Altman plots depicted in Figures 1 to 6, data plotted on the **x-**and **y-axes** represent the **average** and the **difference** between the values, derived from the different measurement techniques respectively**.**

In Figures 1A to 6A, similar colours and shapes represent data from the same individual.

In Figures 1B to 6B, the regression line for the differences between measurement techniques (x-axes) as the parameter changes (y-axes) are depicted.

Figures 1C and 1D represent similar data as in Figures 1A and 1B, but the 3 outliers have been omitted.

Figures 7 to 12arescatter plots depicting the relationship between data measured by the two techniques. The diagonal dashed brown line in these figures represents the line of identity.

For this study, the following measurement techniques were regarded as representing the '**gold standard':**

-Pulmonary artery catheter for cardiac output (CO).

-Oxygen consumption module for oxygen consumption (VO2).

-Blood sample taken from the pulmonary artery catheter for mixed venous saturation (SvO2).

Data collection and demographics (Table 6)

Thirteen patients were enrolled and twenty-eight data sets were collected. Data points are missing for the following reasons:

1. **Poor and/or difficult LiDCO calibration.** Reasons for that include poor initial calibration, changes in vascular resistance, hemodynamic instability, surgeon touching the heart, vasoactive and other drugs. There was one patient in which LiDCO calibration was impossible as continued attempts at calibration could cause Lithium toxicity.
2. **LiDCO sensor problems.** The LiDCO sensor had to be replaced twice during one case, and the readings were probably unreliable.
3. **Mixed venous oxygen sample withdrawal problems.** Mixed venous saturation was 99% and PvCO2 3.1 kPa, while arterial sample was 96% and PaCO2 5.6 kPa in one sample pair. One quality assurance criteria was to ensure that the mixed venous sampling was to draw the blood slowly, to ensure that the venous-arterial carbon dioxide partial pressure difference exceeds 0.5kPa. Therefore, data were rejected.
4. **Unstable patient, requiring intra aortic balloon pump.** This made LiDCO data unusable.
5. **Defective blood gas machine**. In one case, the machine only reported hematocrit and we had to derive the hemoglobin value by dividing by 3.
6. **Exclusion criteria.** There were also two patients that we couldn't include into the study because of contraindications to using LiDCO in them; in one the body mass index was too low and the other had an aortic incompetence.

Patient	Number recordings	Age Years	Gender	Weight kg	Height m	Surgery	Problems encountered
1	0	52	Female	55kg	1,65	CABG[1]	Impossible to calibrate LiDCO
2	2	64	Female	84kg	1,62	CABG[1]	Very big difference between calculated and measured oxygen consumption
3	2	64	Male	45kg	1,64	Femoral-anterior tibial bypass	None
4	2	45	Male	69,3	1,73	Femoral-popliteal and tibial bypass	None
5	3	66	Male	84	1,65	CABG[1]	Initial difficulty with LiDCO calibration
6	3	62	Male	46,5	1,64	CABG[1]	Poor relationship calculated and measured VO2. Couldn't do study post bypass, patient was unstable on balloon pump.
7	3	27	Male	49	1,60	Mitral valve replace-mend	Poor correlation between measured and calculated VO2
8	2	60	Female	66	1,48	CABG[1]	Mixed venous gas withdrawn too rapidly. LiDCO sensors required replacement twice.
9	3	80	Male	72	1,70	CABG[1]	Surgical manipulation of heart with unstable cardiac output and dysrythmias, made LiDCO calibrationunreliable.
10	1	67	Male	74	1,74	Aortic bi-femoral bypass	Poor LiDCO calibration
11	2	42	Male	113	1,79	CABG[1]	None
12	3	29	Male	87,6	1,76	Mitral valve repair	None
13	4	68	Female	73	1,56	Redo CABG[1]	None

Table 6: **Patient demographics and problems encountered:**
[1]CABG cardiac arterial bypass graft

Oxygen consumption [Tables 1, 3, 4, 5 and Figures 2A&2B]

Oxygen consumption measured directly by the gas module and that calculated from PAC derived data were 221 and 169 ml/minute respectively. [Table 3] The **bias-accuracy [limits of agreement]** and **percentage error (PE)** between techniques was +52 [-51 to 156] ml/minute [Table 1] and 27% [Table 5] respectively. In other words, PAC derived oxygen consumption underestimated that measured by the gas module data by an average of 27% or 52 ml/minute. Furthermore, as the 95% confidence interval of the difference in the mean bias-accuracy between techniques [33 to 72ml/minute, Table 1] did not include zero, measurements derived from the two techniques can be considered statistically different.

A statistically significant (exponential) relationship [r^2 = 0.4, Table 4] was observed between the two oxygen consumption techniques. Inspection of graph 2A supports the above finding that the gas module returned higher oxygen consumption measurements then those derived from the PAC.

The 95% confidence interval of the slope of the regression line of the differences [-0,5 to +0,3, Table 1] included zero, and thus we conclude there was no tendency for the differences in oxygen consumption between techniques to change as oxygen consumption changed.

Cardiac output[Tables 1, 3, 4, 5 and Figures 1A&1B]

Cardiac output measured using intermittent thermodilution PAC and LiDCO were 4.3 and 5.1 litres/minute respectively [Table 3]. The **bias-accuracy [limits of agreement]** and **percentage error (PE)** between techniques was -0.82 [-4.4 to 2.7] litres/minute [Table 1] and 26 % respectively [Table 5]. In other words, LiDCO derived cardiac output overestimated that measured using intermittent thermodilution PAC, by an average of 26% or 0.82litres /minute. Furthermore, as the 95% confidence interval of the difference in the mean bias-accuracy between techniques [-1.5 to -0.14 litres/minute, table 1] did not include zero, measurements from the two techniques are considered

statistically different.

A significant (exponential) relationship [r^2 = 0.8, table 4] between the two cardiac output measurement techniques was observed. Inspection of Figure 1A supports the above contention that LiDCO estimated cardiac output was higher than those derived via the PAC.

The 95% confidence interval of the slope of the regression line [table 1] of the differences in cardiac output [-0.8 to -0.4] did not include zero, and thus it can be concluded that the cardiac output estimated by the LiDCO decreased as cardiac output increases.

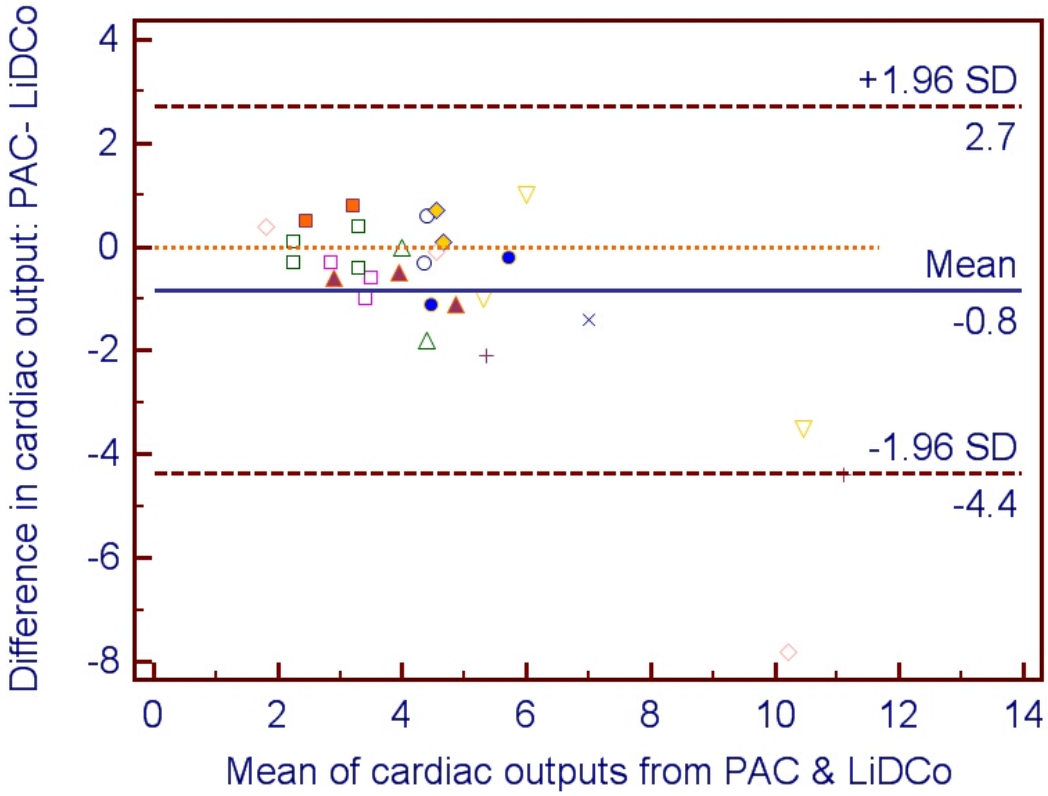
The **precision [**coefficients of variation [CV] and error [CE]] **of** intermittent bolus thermodilution PAC derived **cardiac output measurements** [Table 5]were5.7 **[95% confidence interval** 4.3 to 7.1] and 3.0 [**95% confidence interval** 2.3 to 3.8]% respectively.

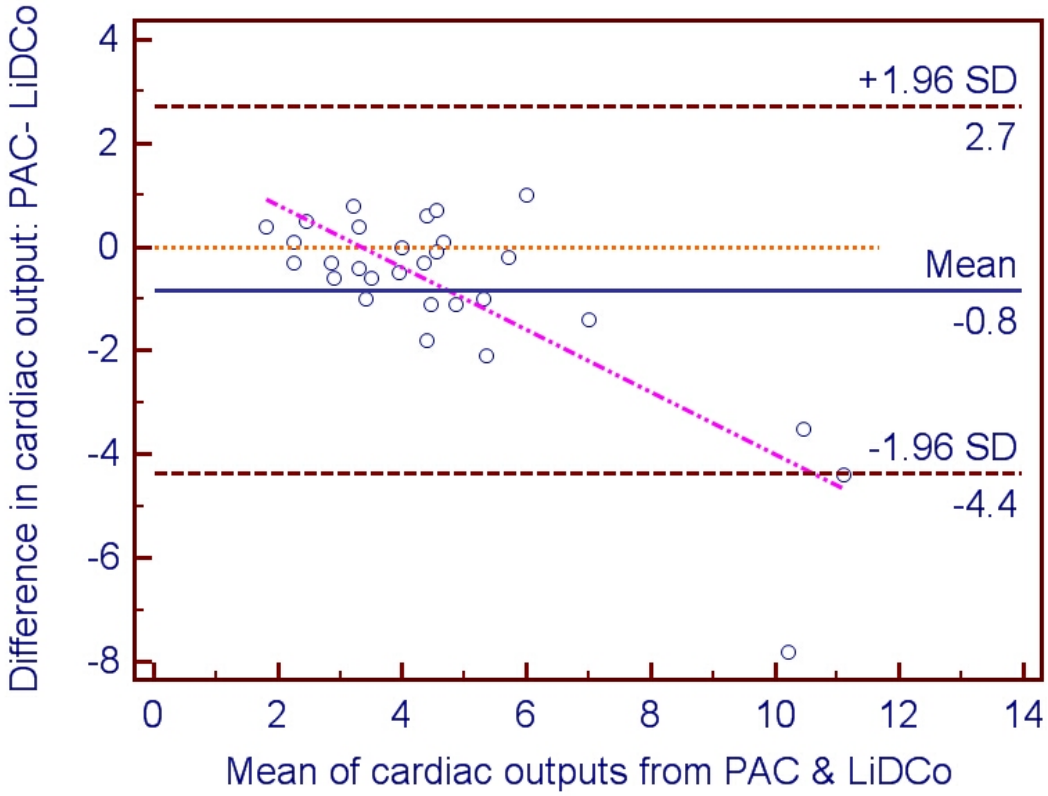
Venous oxygenation (Tables 1,3,4,5 and Figures 3,4,5)
Measured and calculated **venous oxygenation data** [Table 3] (CvO2, SvO2, PvO2 and PvO2 corrected for temperature and pH) were8.9 and 8.0 ml/100ml, 66.5 and 59.0 %, 5.1 and 4.3, and 4.4 kPa respectively. The **bias-accuracy [limits of agreement]** (CvO2, SvO2, PvO2 and PvO2 corrected for temperature and pH) [Table 1] between techniques was 0.9 [0.3 to 1.5] ml/100ml, 7.6 [3 to 13] %, 0.8 [0.4 to 1.1] and 0.5 (0.1 to 0.9) kPa respectively. The percentage errors (CvO2, SvO2, PvO2 and PvO2 corrected for temperature and pH) were 24.2, 24.0, 26.3 and 12.0% respectively [Table 5]. None of the 95% confidence intervals of the difference in the mean bias-accuracy between (calculated and measured) techniques for determining CvO2 [0.3 to 1.5ml/100ml], SvO2 [3 to 13%] and PvO2 [0.4 to 1.1Kpa] [table 1] included zero; measurements from the two techniques are thus considered statistically different.

Significant linear relationships [r^2 = 0.7, 0.2, 0.2 and 0.2] between techniques

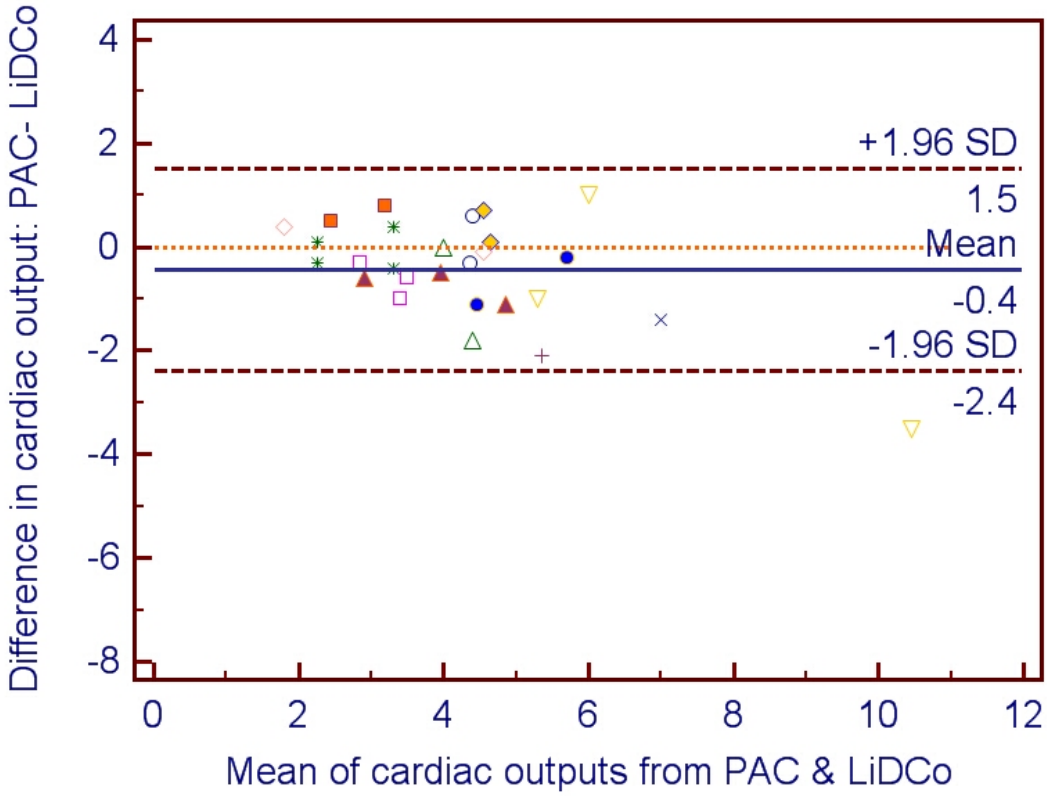
of determining **venous oxygenation data** (CvO2, SvO2, PvO2, and PvO2 corrected for temperature and pH respectively) [Table 4] was observed.

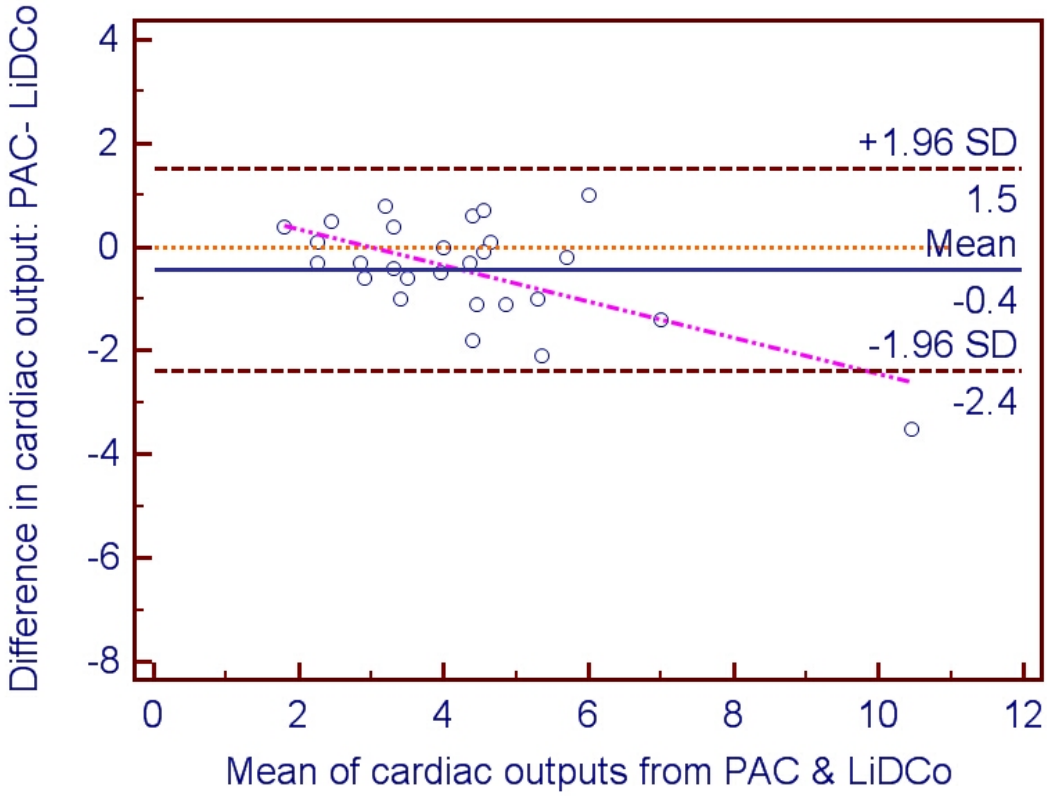
The 95% confidence interval of the slope of the regression line [Table 1] of the differences for CvO2 [-0.5 to -0.1], SvO2 [-1.2 to -0.2], and PvO2 corrected for temperature and pH [-1.1 to -0.1] does not include zero, and thus the differences between the measured and calculated CvO2, SvO2 and PvO2 (corrected for temperature and pH) changes as CvO2 and SvO2 increase. However, the 95% confidence interval of the slope of the regression line of the differences for PvO2 [-0.9 to 0.1] does include zero, and we conclude there was no tendency for the differences in SvO2 (PAC and calculated) to change as SvO2 changed.





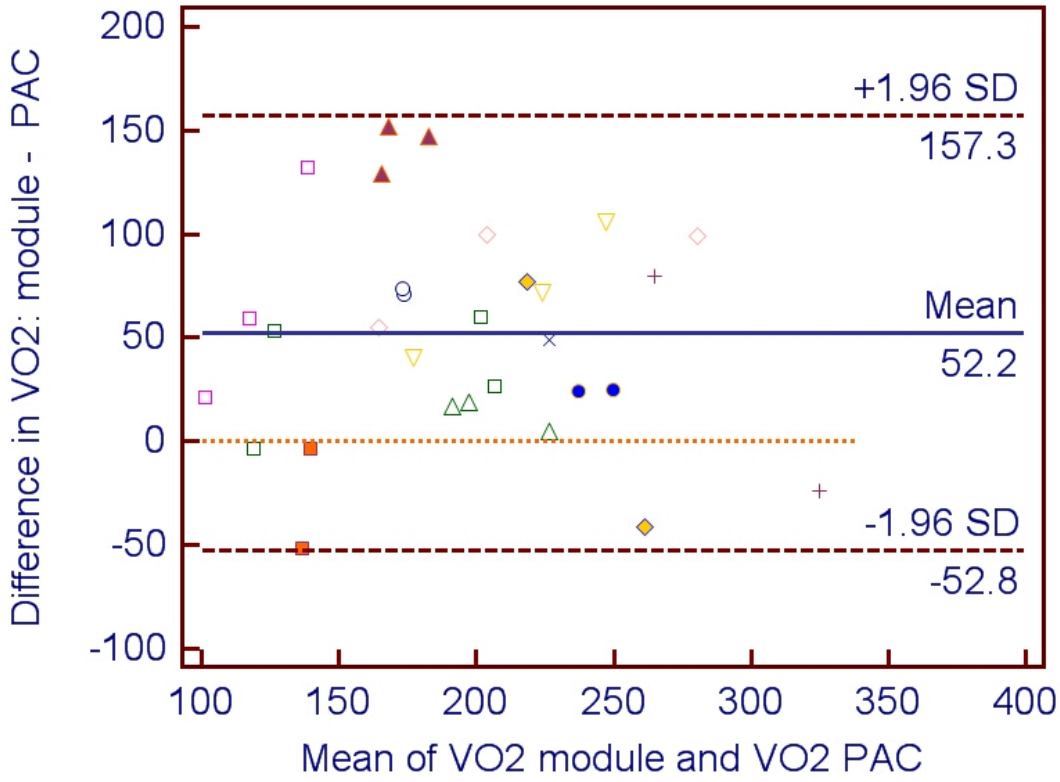
Figures 1A (top) **and 1B** (bottom). Bland Altman plots for cardiac output (See text in "Results" section for legend and explanation)

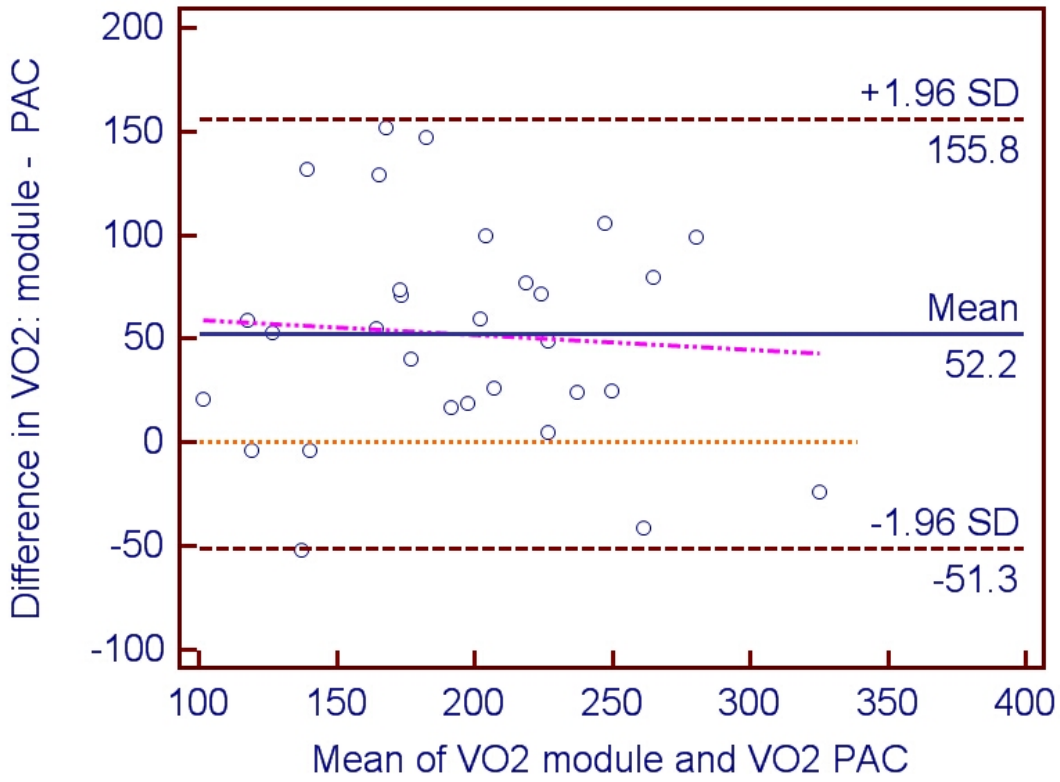




Figures 1C (top) **and 1D** (bottom). Bland Altman plots for cardiac output with outliers deleted

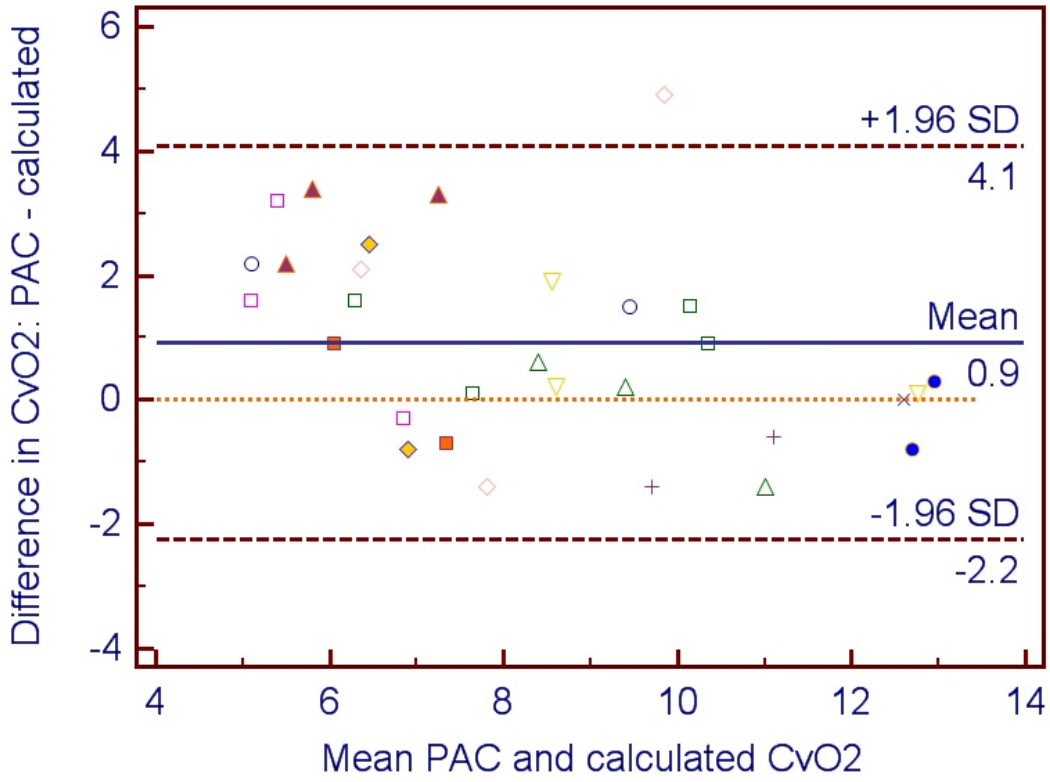
(See text in “Results” section for legend and explanation)

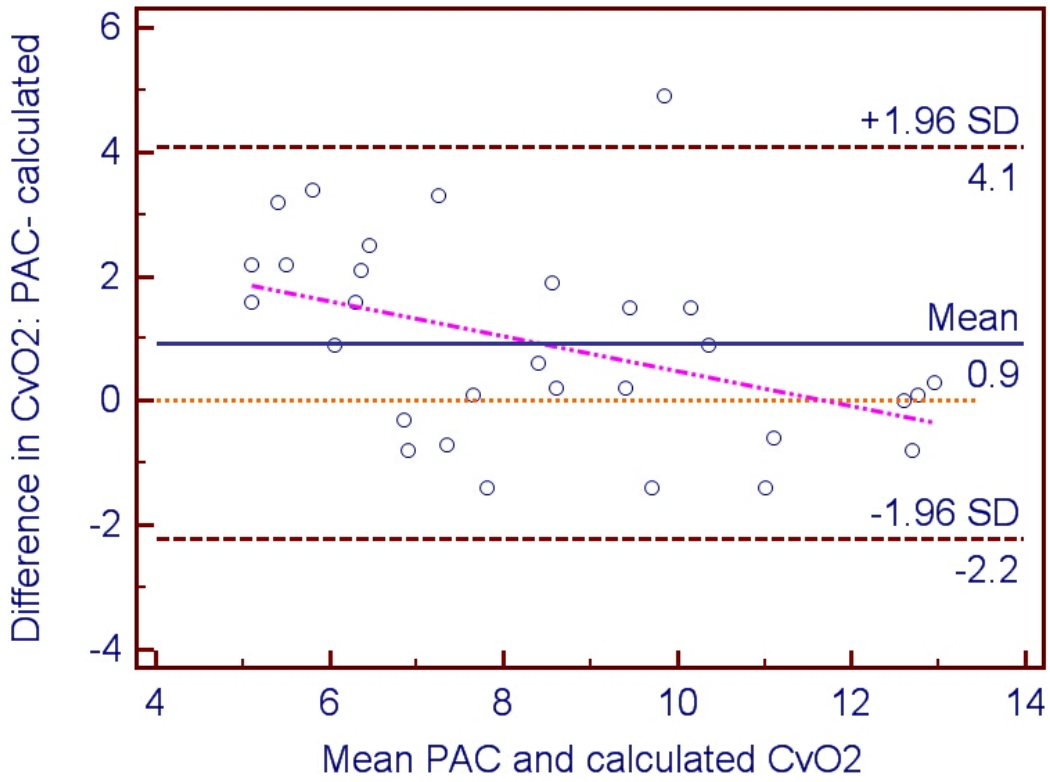




Figures 2A (top) **and 2B** (bottom) .Bland Altman plots for oxygen consumption

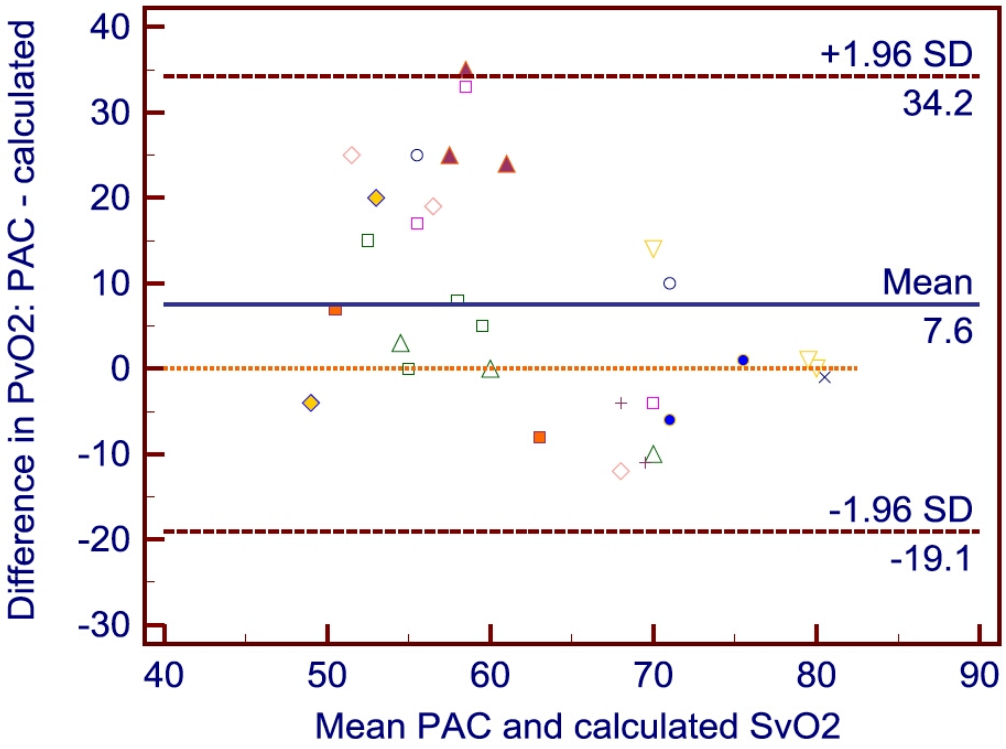
(See text in “Results” section for legend and explanation)

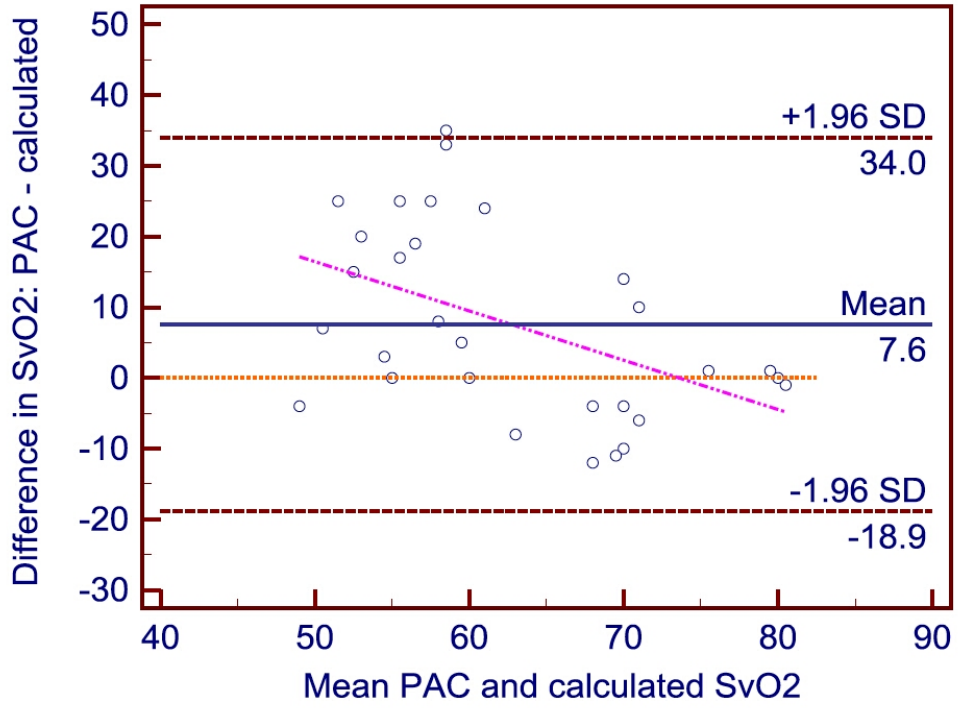




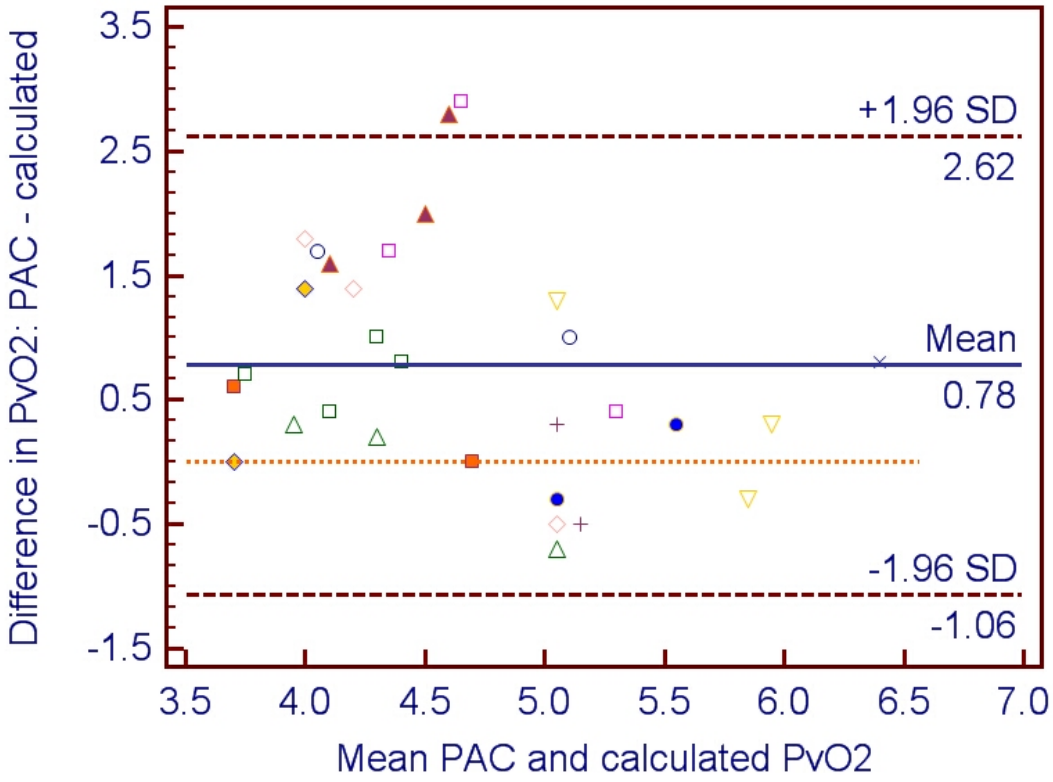
Figures 3A (Top) **and 3B** (bottom). Bland Altman plots for mixed venous oxygen content

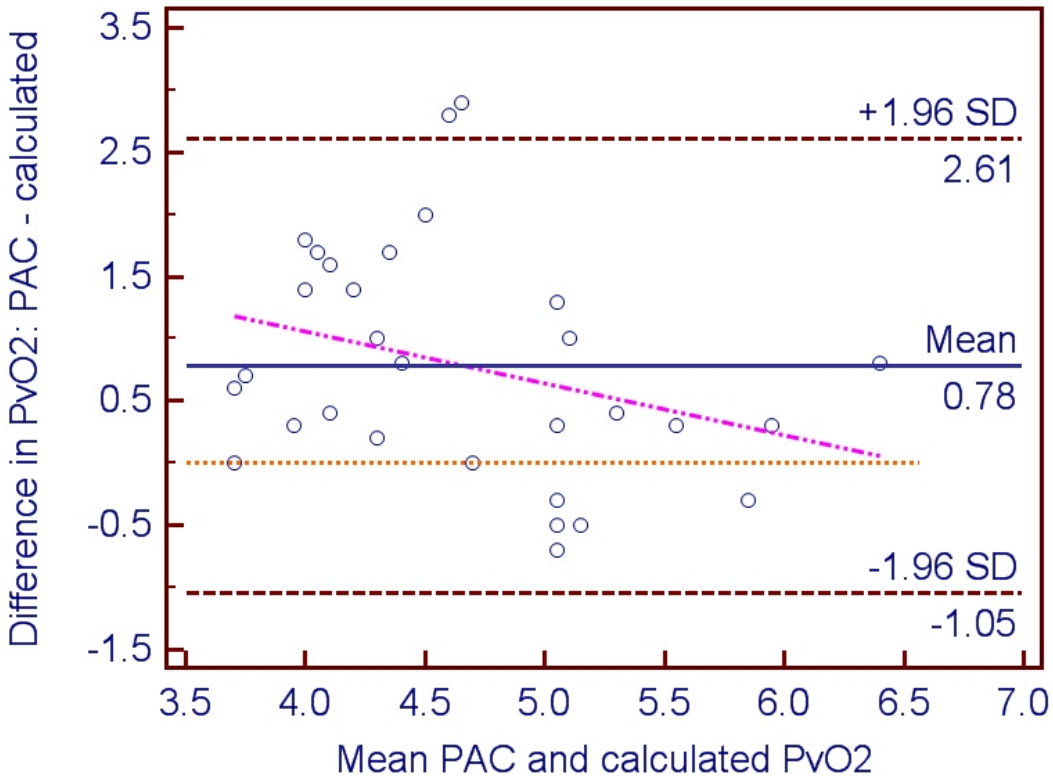
(See text in “Results” section for legend and explanation)





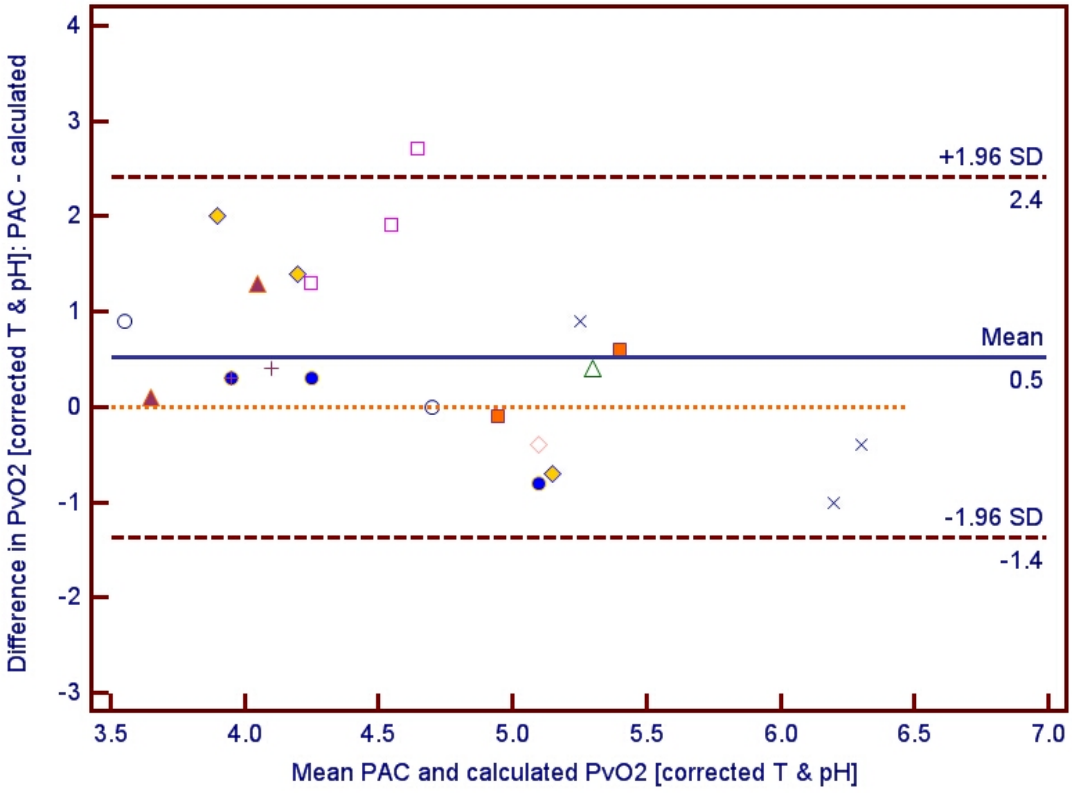
Figures 4A (Top) **and 4B** (bottom). Bland Altman plots for mixed venous oxygen saturation
(See text in "Results" section for legend and explanation)

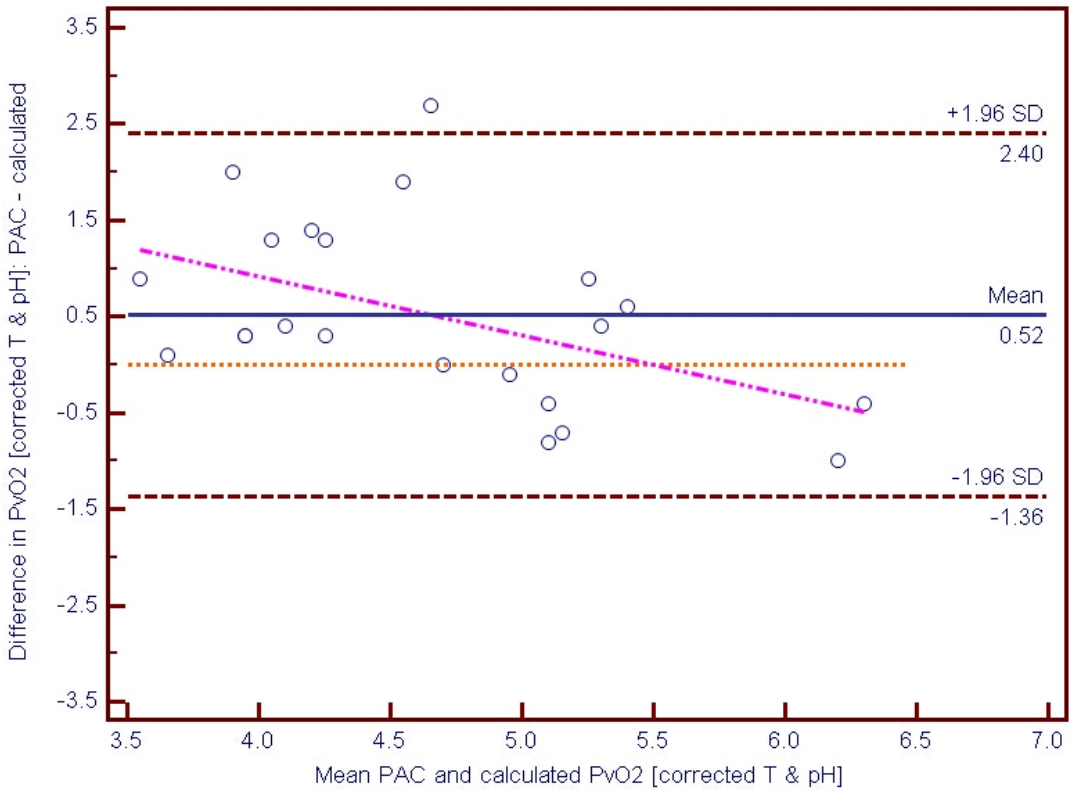




Figures 5A (Top) **and 5B** (bottom). Bland Altman plots for mixed venous oxygen partial pressure.

(See text in "Results" section for legend and explanation)





Figures 6A (Top) **and 6B** (bottom). Bland Altman plots for mixed venous

oxygen partial pressure, corrected for temperature and pH.

(See text in "Results" section for legend and explanation)

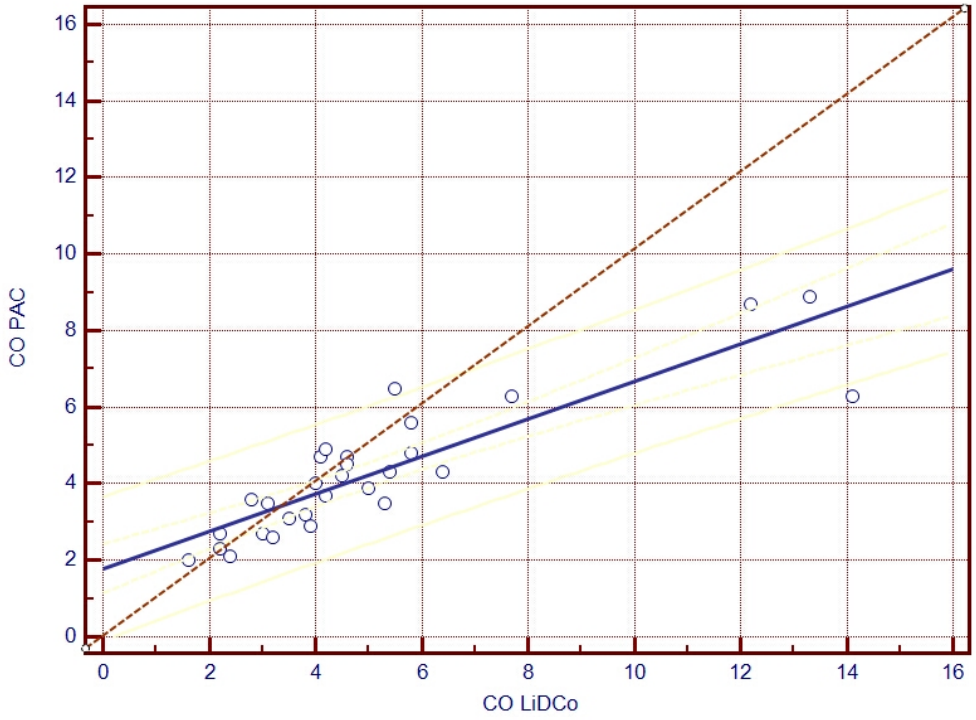


Figure 7.
Scatter plot of cardiac output determined by the two techniques
(See text in "Results" section for legend)

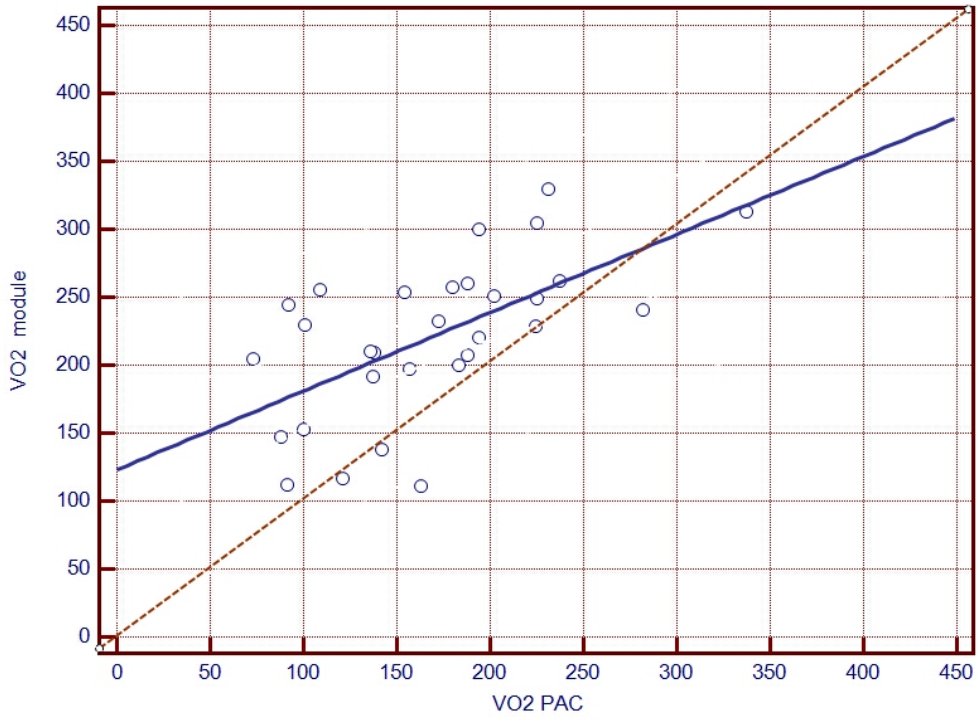


Figure 8.
Scatter plot of oxygen consumption determined by the two techniques
(See text in "Results" section for legend)

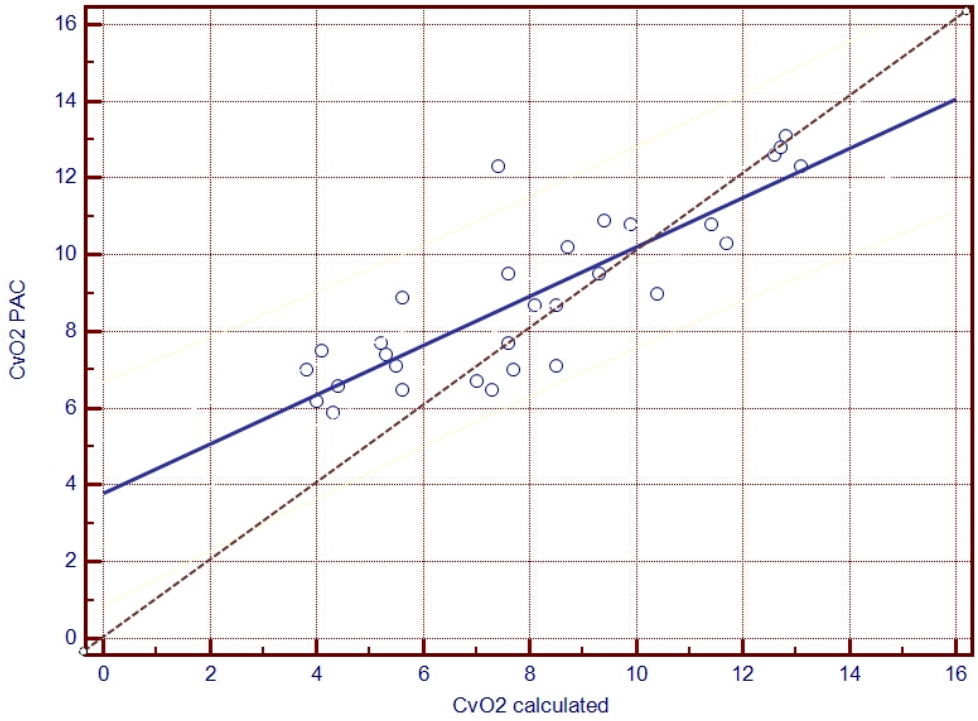


Figure 9.
Scatter plot of mixed venous oxygen content determined by the two techniques
(See text in "Results" section for legend)

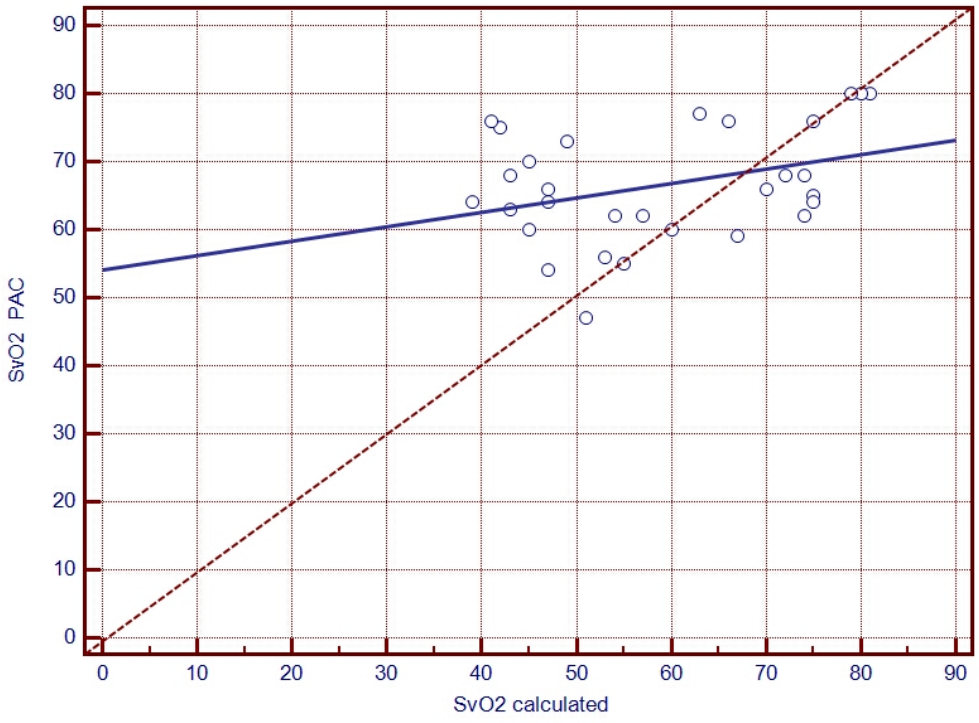


Figure 10.
Scatter plot of mixed venous oxygen saturation determined by the two techniques
(See text in "Results" section for legend)

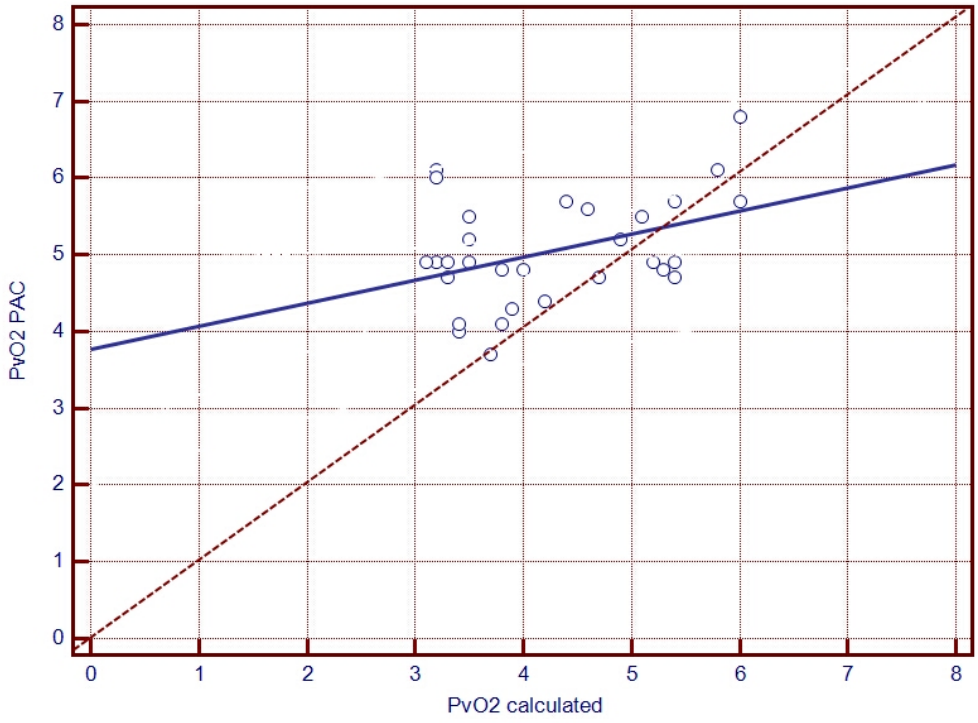


Figure 11.
Scatter plot of mixed venous oxygen partial pressure determined by the two techniques
(See text in "Results" section for legend)

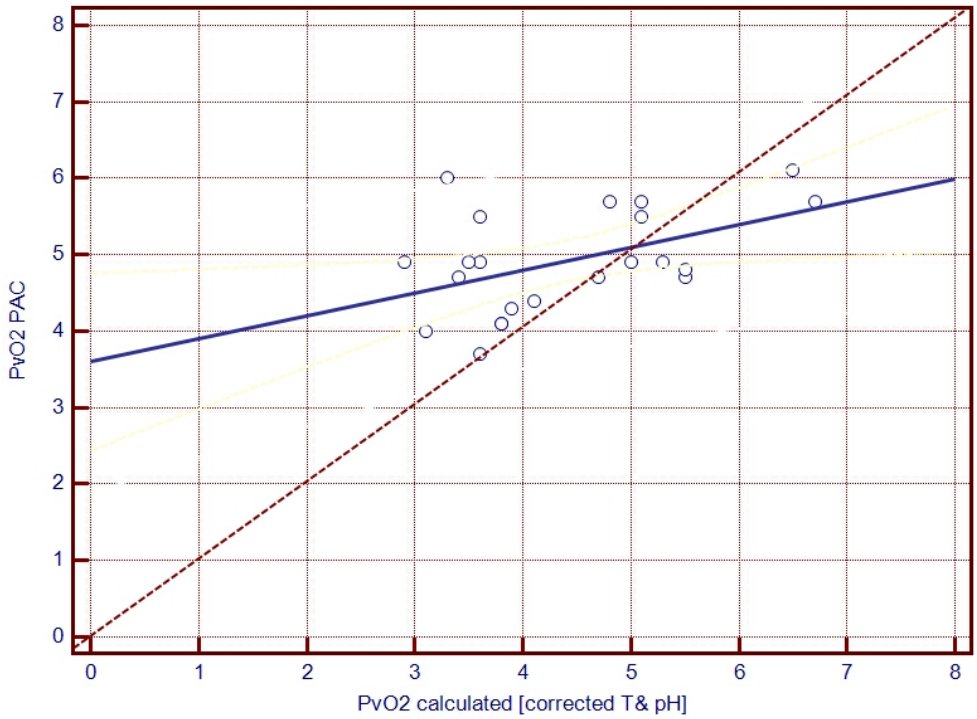


Figure 12.
Scatter plot of mixed venous oxygen partial pressure corrected for pH and temperature determined by the two techniques
(See text in "Results" section for legend)

	Units	N	Mean difference [95% CI]	SD	1,96 SD [95% CI]	-1,96 SD [95% CI]	Regression line of differences	95% CI of slope of regression line
VO2	ml/minute	30	52 [33 to 72]	54	156 [122 to 190]	-51,3 [-85 to -17]	y = 66,0 + -0,1x	-0,5 to 0,3
CO	litres/minute	29	-0,8 [-1,5 to -0,14]	1,8	2,7 [1,5 to 3,9]	-4,4 [-5,6 to -3,2]	y =2 + -0,6x	-0,8 to -0,4
CO (no outliers)	litres/minute	27	-0,4 [-0,8 to -0,04]	1,0	1,5 [0,8 to 2,2]	-2,4 [-3,1 to -1,7]	y = 1,1 + -0,4 x	-0,5 to -0,2
CvO2	ml O2/100ml	30	0,9 [0,3 to 1,5]	1,6	4,1 [3,0 to 5,1]	-2,4 [-3,1 to -1,7]	y = 3,3 + -0,3x	-0,5 to -0,1
SvO2	%	30	7,6 [3 to 13]	14	34 [25 to 43]	-19 [-28 to -10]	y = 51,3 + -0,7x	-1,2 to -0,2
PvO2	kPa	30	0,8 [0,4 to 1,1]	0,9	2,6 [2,0 to 3,2]	-1,1 [-1,7 to -0,45]	y = 2,8 + -0,5x	-0,9 to 0,1
PvO2 (Corr. pH, T)	kPa	22	0,5 [0,1 to 0,9]	1,0	2,4 [1,7 to 3,1]	-1,4 [-2,1 to -0,6]	y = 3,4 + -0,6 x	-1,1 to -0,1

Table 1: Bland Altman plots for differences between measurement techniques for various parameters. (See text in "Results" section for legend and explanation)

Legend: 1,96 SD and-1,96 SD represent the upper and lower limits of agreement respectively

'corr. pH, T' represents corrected for pH and temperature

	Units	n	Lowest value	Median	Highest value
VO2	ml/minute	30	-52	**54**	152
CO	litres/minute	29	-7.8	**-0.3**	1.0
CvO2	ml O2/100ml	30	-1.4	**0.75**	4.9
SvO2	%	30	-12	**4**	35
PvO2	kPa	30	-0.7	**0.65**	2.9
PvO2 (Corr. pH, T)	kPa	22	-1	**0.35**	-2.7

Table 2: Mountain plots of the differences between measurement techniques for various parameters. (See text in "Results" section for legend and explanation)

Legend: 'corr. pH, T' represents corrected for pH and temperature

	Units	N	Mean	95% CI of the mean	S.D.
CO PAC	litres/minute	30	4.3	3.6 to 4.9	1.7
CO LiDCo	litres/minute	29	5.1	3.9 to 6.3	3.1
VO_2 module	ml/minute	30	221	199 to 243	58.0
VO_2 c alculated	ml/minute	30	169	146 to 192	61.4
CvO_2 PAC	ml O2/100ml	30	8.9	8.1 to 9.7	2.2
CvO_2 calculated	ml O2/100ml	30	8.0	6.9 to 9.1	2.9
SvO_2 PAC	%	30	66.5	63.4 to 69.7	8.5
SvO_2 calculated	%	30	59.0	53.8 to 64.1	13.8
PvO_2 PAC	kPa	30	5.1	4.8 to 5.3	0.7
PvO_2 calculated	kPa	30	4.3	3.9 to 4.6	1.0
PvO_2[Corr. pH , T]	kPa	22	4.4	3.9 to 4.9	1.1

Table 3: Descriptive statistics of the measured and calculated parameters. (See text in "Results" section for legend and explanation)

Legend: 'corr. pH, T' represents corrected for pH and temperature

	Units	N	r	r^2	p	Regression Equation (Excel)
CO	litres /minute	29	0.9	0.8	<0.0001	y = 1.6 x to 1.6
VO_2	ml/minute	30	0.6	0.4	0.0003	$y = 0.003x^2-0.6x + 150$
CvO_2	ml O2/100ml	30	0.8	0.7	<0.0001	y = 1.1 x - 1.7
SvO_2	%	30	0.4	0.2	0.06	y = 0.6x + 21.3
PvO_2	kPa	30	0.4	0.2	0.027	y = 0.5x + 1.5
PvO_2[Corr. pH, T]	kPa	22	0.5	0.2	0.024	y = 0.8x + 0.6

Table 4: Correlation coefficients between different measurement techniques for various parameters. (See text in "Results" section for legend and explanation)

Legend: 'corr. pH, T' represents corrected for pH and temperature

	Units	N	Mean %	95% CI of mean	S.D.
Accuracy PvO_2	%Error	30	26.3	16.8 to 35.9	25.6
Accuracy PvO_2[Corr. pH, temp]	% Error	30	12.0	7.2 to 16.9	13.1

Table5: Accuracy [bias] and precision for PvO2.

(See text in "Results" section for legend and explanation)

Legend: 'Corr. pH, temp' represents corrected for pH and temperature

Discussion

Overview

This study was designed to investigate whether mixed venous oxygenation (partial pressure, saturation and content) can be determined by using minimally invasive techniques of measuring cardiac output and oxygen consumption. The reasoning behind the study was while minimally invasive measures of cardiac output are increasingly popular, they cannot provide simultaneous measurements of mixed venous oxygenation as does the pulmonary artery catheter. Furthermore, although popularized after Rivers and colleagues publication regarding management of septic patients, central cannot substitute for mixed venous oxygenation values particularly in anesthetized, sedated and critically ill patients. (2;8;9;10)

In this study, the minimally invasive techniques included cardiac output measurement using a lithium dilution technique (LiDCo®) and oxygen consumption calculated using a calorimetric device. Arterial oxygen content was calculated using blood withdrawn from an arterial catheter. These 3 parameters were inputted into Fick's equation relating oxygen consumption, cardiac output and the arterio-venous oxygen content difference, and solved for venous oxygen content. We used a standard oxygen dissociation curve formula [Appendix G] to setup a spreadsheet relating a range of oxygen partial pressures, saturations, hemoglobin concentrations and oxygen con tent. This spreadsheet was then used as a lookup table to relate venous oxygen content to venous oxygen saturation and partial pressure at the measured hemoglobin concentrations. The calculated values were compared to those obtained from sampling true mixed venous blood.

The study concluded that mixed venous oxygenation could not be estimated accurately enough using the minimally invasive methods employed.

The reasons for our conclusion

Despite small (12.0 to 26.3 %) differences between measurements in individual patients, parameters of mixed venous oxygenation measured by the different techniques were statistically different. Furthermore, we considered that the magnitude of these differences could adversely impact clinical decision-making. Reasons for the difference in measured and calculated venous oxygenation data might be due to combinations of the following:

1. Factors influencing the calculation of oxygen content (CaO2 and CvO2).
2. Different aspects of individual parameters cardiac output and oxygen consumption.
3. Technical errors.
4. Factors influencing the oxygen dissociation curve (ODC).

Calculation of arterial and venous oxygen contents:

The oxygen content of blood can be calculated by the following formula:

CaO_2= [Hb X Saturation/100 X 1,39] + 0,003PaO_2(kPa)

Inaccuracies in measurement of **hemoglobin concentration, oxygen saturation** and **partial pressure of oxygen** would deleteriously affect this calculation. These variables are likely to be precise, because we measured it using a dedicated, calibrated blood gas machine. Factors possibly contributing to imprecision and inaccuracy in blood gas measurements include **inherent drift characteristics of the blood gas electrodes**, **contamination** from residual material within the measuring chamber, and **instrument variation** over time. Therefore, quality control of these instruments is critical. These problems were minimized by the use of regularly calibrated, disposable blood gas packs.

Gas bubbles in the blood sample can cause inaccurate results. Contamination of the sample with room air will result in abnormally low carbon dioxide and possibly elevated oxygen levels, and a concurrent elevation in pH. **Delaying analysis**, without chilling the sample, may result in

inaccurately low oxygen and high carbon dioxide levels as a result of ongoing cellular respiration. To avoid these problems, we analyzed blood gases within 5 minutes of sample withdrawal. Withdrawing the sample from an indwelling arterial catheter using luer slip connectors largely eliminated the possibility of contamination with bubbles; nonetheless we inspected the specimens after withdrawal and eliminated all visible gas bubbles. Indeed, if there were more than one or two easily eliminated bubbles, the sample was discarded.

Electrode signals are dependent upon **temperature** as well as concentration, and all measurements are performed at 37°C. Since the in vivo pH and levels of oxygen and carbon dioxide are temperature dependent, results may need to be adjusted for the patient's actual temperature. Modern automated blood gas analyzers are capable of reporting values at either 37ºC, the temperature at which the values are measured by the machine, or at the patient's temperature. Whether pH, PCO2, and PO2 should be interpreted as “pH-stat" or “alpha-stat" methods is controversial. When employing pH-stat, blood gas parameters are "corrected" to the patient's actual body temperature, while “alpha-stat" analysis entails that the results are interpreted uncorrected. We conventionally use “alpha-stat" method.

The use of (acidic) **heparin** added to the syringe as an anticoagulant may cause small changes in pH. Furthermore, depending on the relative volumes of **heparin** and blood, the dilutional effect of the heparin solution can cause significant reductions in the PCO2. We kept the amount of heparin solution to a minimum, and always sampled more than two millilitres of blood.

The amount of oxygen able to bind to haemoglobin (Hoeft's constant) was assumed to be1.39 ml oxygen per millilitre of blood. This is the theoretical maximum and values as low as1.34 have been reported. As stated before, w e do not believe this is to be of significance as this fixed value was used in all our analyses. We also do not believe that repeating all the calculations with

other values would add value to this study.

Oxygen consumption

PAC derived oxygen consumption underestimated that measured by the gas module by an average of 27%. This was not surprising because the "reverse Fick" method employed by the PAC systematically underestimates whole body oxygen consumption. The reason for this is that intra-pulmonary oxygen consumption, comprising 20 to 32% of total body oxygen consumption, is excluded by this method. (42) Indeed, because of this limitation, indirect calorimetry is considered the gold standard for determining oxygen consumption. [30-32]

In our study, oxygen consumption was the parameter having the largest percentage error (27%) and difference between the Bland Altman upper and lower limits of agreement. This scatter was probably the major reason for the discrepancy between the mixed venous oxygenation parameters measured by the two techniques. Prior studies utilizing different methods of oxygen consumption have demonstrated both good[51-53] and poor[52-56] agreement between techniques. The important reasons for the discrepancies between the reverse and direct Fick methods of determining oxygen consumption in this study remain unclear, but might be due to combinations of the factors delineated below.

Limitations of calculating oxygen consumption using the "reverse Fick" PAC method: [52, 53]

1. Only snapshot values are possible for bolus thermodilution. The method encompasses performing 3 to 4 intermittent cardiac output determinations over approximately as many minutes. Thereafter mixed venous blood is sampled. Thus the timeline of this method contains inherent differences compared to the "direct Fick" method, the latter calculating oxygen consumption on a breath-by-breath basis.
2. Pulmonary oxygen consumption is excluded when using the reverse Fick

method.

3. Many variables are involved in the reverse Fick calculations:

   $VO_2 = CO (CaO_2 – CvO_2)$; and

   Oxygen content = [Hb x Saturation X 1,39] + [0,0031 PaO_2 (kPa)].

   Measurement inaccuracies of any of the parameters used in the above 2 calculations will produce cumulative, up to 20%, [34, 35] errors in the calculation of oxygen consumption. [52, 53]

The following factors might lead to inaccurate oxygen consumption measurements when using indirect calorimetry:

1. **High-inspired oxygen concentration ($FiO_2 > 0.7$):** Oxygen consumption is calculated from the difference between inspiratory and expiratory oxygen fractions. Small errors in these measurements magnify as oxygen concentration increases with potential inaccurate VO_2 values. (40;44)
2. **Achievement of steady state:** The achievement of a steady state during indirect calorimetry measurements is necessary to reduce error and ensure accuracy during the measurement. Steady state is defined as 5 consecutive minutes during which oxygen consumption and carbon dioxide production vary by less than 10%. [57]
3. **System leaks:** Leaks in the ventilator circuit, around tracheal tube cuffs or un-cuffed tubes, through a chest tubes or broncho-pleural fistula, prevent collection of expired gases and cause erroneously low VO_2 readings. (40)
4. **Water in the breathing system tubing[58] and tidal volume measurement inaccuracies:** Excess water and condensation in the spirometry tubing increases flow resistance in the pneumotachograph, which causes tidal volume (and thus VO_2) overestimation.[48]
5. **Respiratory rate exceeding 35 breaths per minute and abnormally high airway pressures**(40;44): The M-COVX™ module we used, relies on tidal volume measurement for oxygen consumption calculation. The pneumotachograph built into the M-COVX™ module derives the tidal volume from the pressure difference across a fixed orifice. Hyperventilation and high airway pressures might cause inaccurate

readings by influencing tidal volume readings.

We specifically tried to avoid the above issues as far as possible during the utilisation of indirect calorimetry in our study. Another consideration was that, if the tidal volume measurements incorporated by the calorimetry module were not entirely accurate, this could have influenced the accuracy of the oxygen consumption measurements.

From our results, it is evident that pulmonary artery catheter derived oxygen consumption underestimated that measured by the gas module data by an average of **27%** or 52 ml/minute. This fits in with what is known about the difference in oxygen consumption measured by indirect calorimetry and the PAC. According to the M-COVX™ module User's Reference Manual, gas calibration is only required every 12 months; due to the unit's design, more frequent calibration is not needed. The South African supplier services our modules yearly according to manufacturer's specifications and the drift between yearly calibrations is approximately 0.01 to 0.02% (personal communication with Medhold service department, South Africa).

Cardiac output:

In our study, a strong coefficient of determination (r^2 = 0.8) was observed between cardiac output measured by the different techniques. LiDCO® derived cardiac output did not differ statistically from that measured using intermittent thermodilution PAC. Furthermore, inspection of the data scatter suggests that LiDCO® derived cardiac output was clinically acceptable. We calibrated the LiDCO® and subsequently recorded parameters under "clinically stable" hemodynamic conditions. The problem is that the LiDCO® device needs repeat calibration following hemodynamic changes. [59-61] Another potential problem is the influence of vasopressors and other drugs on LiDCO® accuracy.[62]

The precision of the thermodilution cardiac output measurements as

determined by the coefficients of variation [CV][1] and error [CE][2] were 5.7 [95% confidence interval 4.3 to 7.1] and 3.0 [95% confidence interval 2.3 to 3.8] % respectively. This represents a small coefficient of variation, and indicates that the thermodilution cardiac output measurements are reproducible and reliable.[64, 65]

It is interesting that cardiac output estimated by the LiDCO® decreased as PAC derived cardiac output increased. While speculative, the most probable reason for this systematic inaccuracy is that higher cardiac outputs resulted in inaccuracies in LiDCO® calibration. The consequence of such a systematic error would likely be that at higher cardiac outputs, the erroneous reporting of lower values will lead to a falsely low calculated mixed venous oxygen content (CvO2 = CaO2 - VO2/CO) compared to the directly measured value.

Factors that could contribute to inaccurate cardiac output readings:

Limitations of measuring cardiac output using the pulmonary artery catheter [66, 67]

1. Long injectate times, less than 2 seconds being ideal.
2. Low cardiac output states.
3. Intra cardiac shunts.
4. Severe tricuspid and pulmonary valve regurgitation.
5. Large temperature shifts

Limitations of measuring cardiac output using LiDCO™ [37]

1. PoorLiDCO™ calibration.

---

[1]**Coefficient of Variation** [C_v] is the percentage variation of the mean values and is calculated as Standard Deviation / Mean. It is used to compare the variability of two or more measurements. If the coefficient of variation is large it indicates that the group is more variable and it is less stable or less uniform.

[2]The measure of the quality of a series of quantitative measurements is called the **coefficient of error**, or CE. [CE =CV of single measurements/√n.]

2. Influence of vasoactive and other drugs. [62, 68]
3. Hemodynamic changes and change in systemic vascular resistance.[59-61, 69]
4. Severe peripheral arterial vasoconstriction.
5. Undiagnosed aortic valve regurgitation.
6. Patient treated with aortic balloon pumps.

Of the above-mentioned factors, the most relevant in our study would be the influence of hemodynamic changes secondary to changes in systemic vascular resistance, bleeding, administration of vasopressors and the effect of drugs on LiDCO® calibration. All study participants underwent cardiothoracic or vascular surgery, and therefore the major factor affecting LiDCO® calibration would likely have been hemodynamic changes. Even though recalibration is suggested only every 24 hours,[49] we were concerned that changes in impedance after bypass and unclamping of the aorta will influence LiDCO® calibration, therefore we initiated recalibrated after these events.[60, 61] The clinician's dilemma is that when cardiac output monitoring is needed, hemodynamic changes indicating the need for recalibration are not always apparent. This issue, coupled with the limitations on the total permissible lithium dose, questions the "all weather reliability" of LiDCO® to estimate of cardiac output. Indeed, we specified that our comparisons between techniques be performed only during periods of hemodynamic stability determined by constant blood pressure, vasopressor and fluid requirements. Despite the limitation of intermittent thermodilution in that it only provides snapshots, it remains a relatively reliable technique compared to newer methods that measure cardiac output.[70]

Most of our patients were receiving infusions of vasopressor at some time during the surgical procedure. Although we didn't specifically interrogate the effect of vasopressors on the relationship between PAC and LiDCO® derived

cardiac output, this represents a potential reason for discrepancies between the two measurement techniques.[62, 68] However, we maintained constant values of vasopressor infusions during both the calibration and measurement periods.

Drugs other than vasopressors might also influence LiDCO® accuracy. Recently published research[71] indicates that unexpected voltage changes occur when the lithium sensor is exposed to clinically relevant concentrations of clonidine, dexmedetomidine, medetomidine, ketamine, S-ketamine, lignocaine, and/or rocuronium. The problem is that the expected voltage induced changes that accompany the dose of lithium associated with a particular cardiac output may be affected by these drugs. Indeed, many of our patients received rocuronium, one of the drugs reported to influence the lithium-induced voltage changes. However, we waited at least 30 minutes after rocuronium administration before attempting LiDCO® calibration. This delay would hopefully have ameliorated the effects thereof on the lithium sensor. It is unlikely that rocuronium was responsible for the LiDCO® underestimation at higher cardiac outputs as the above-mentioned drugs increase the LiDCO® estimated cardiac output. [71]

Even though the above-mentioned factors needed consideration, the LiDCO® estimated cardiac output measured by intermittent thermodilution relatively reliably. The main reason that we couldn't estimate venous oxygenation accurately was not because of the different methods of measuring cardiac output employed in this study.

Technical aspects that may have influenced the results:

Another issue that might have affected our results, are the time differences and averaging employed in this study for measurement of cardiac output, oxygen consumption and blood gas sampling.

Cardiac output: The PAC derived cardiac output was specified as the

average of the 3 cardiac output determinations measured using intermittent thermodilution. The LiDCO® derived cardiac output was specified to be the average of the cardiac outputs measured during the minute preceding the first thermodilution cardiac output.

Oxygen consumption: Indirect calorimetry (breath-by-breath) measurements of -oxygen consumption were averaged over the 60 seconds preceding the first thermodilution cardiac output.

Blood sampling: Mixed venous and arterial blood sampling took place only after completion of the intermittent thermodilution triplicate cardiac output measurements.

It is thus clear that the calculated and the directly measured venous o xygenation parameters describe two closely linked, but different, time periods. Unfortunately, the time differences were inevitable as we couldn't measure and estimate simultaneously for the following reasons:

- It is not possible to sample mixed venous blood and simultaneously measure cardiac output using thermodilution.
- We didn't yet, at the time the study was conducted, have access to the modified PAC whereby mixed venous oxygen saturation can be continuously measured.
- Furthermore, arterial blood cannot be sampled simultaneously with performance of LiDCO cardiac output measurements unless a second arterial catheter had been inserted.

However, as mentioned, we also only performed the study measurements during periods of hemodynamic stability. This was defined as no observed or expected changes in the blood pressure, no new surgical intervention was planned and the inotrope, vasopressor and/or vasodilator requirements were not changed or expected to change. Furthermore, during the period of measurement and estimation, only maintenance and no rapid administration of fluid was required.

The precision [coefficients of variation and error] of the VO2 data could not be

determined for two reasons:

- Both the VO2 and LiDCO report output data approximately every 15 milliseconds. Nonetheless, the devices cannot measure the parameters that frequently and CE or CV estimations will produce data that appears too precise.
- For us to estimate precision, we would have needed to measure VO2 repeatedly over a short period of stability using the different techniques. Such an attempt would have been too labor intensive and potentially complicated by technical errors such as too fast withdrawal of mixed venous blood with its associated errors.

Venous oxygenation data and factors influencing the position of the oxygen dissociation curve:

The primary endpoint of this study was to determine the ability to calculate venous oxygenation parameters (CvO2, SvO2, PvO2) using minimally and non-invasive techniques during cardiac and vascular surgery.

Mixed venous oxygen content (CvO2) was calculated using Fick's equation for whole body oxygen flux**.** Inaccuracies in measurement of any of the variables [arterial oxygen content, oxygen consumption and/or cardiac output] would influence the mixed venous oxygen content calculation. The above discussion details that our measurements were relatively accurate when employing the minimally invasive techniques for determining cardiac output, arterial oxygenation and hemoglobin concentration. The major reason for our failure to accurately predict venous oxygenation was the scatter and differences in oxygen consumption returned by the measurement methods. What can be added to this discussion is because, on average, the calorimetric method overestimated oxygen consumption, the experimental method would be expected to underestimate measured venous oxygen content. This indeed occurred in this study.

SvO2 and PvO2 were derived from the calculated CvO2 with the help of an Excel spreadsheet [Appendix G] and lookup table. Even with accurate hemoglobin concentrations, the derived mixed venous saturation and partial pressures might be inaccurate because of the fixed position of the oxygen dissociation curve in the look-up table. This **"fixed" position of the oxygen dissociation curve** in the look-up table does not take into account factors affecting the P50 (position of the oxygen dissociation curve). These factors typically include temperature, carbon dioxide partial pressures, pH, carbon monoxide concentrations, and transfusion of stored bank blood.(41) Surgical procedures in our study included coronary artery bypass grafting, valve replacement and vascular surgery during which factors affecting the position of the P50 of the oxygen dissociation curve typically occur. However, the differences between techniques were not improved if venous oxygenation was indeed corrected for pH and temperature. Another factor to consider is the **mixed venous point** on the **oxygen dissociation curve**. It is important to note that the mixed venous point (pO2 40 mm Hg and hemoglobin saturation 75%) does not really lie on the normal **oxygen dissociation curve**. The increased pCO2 and decreased pH in mixed venous blood mean that the mixed venous point must lay on a slightly right shifted, rather than a standard **oxygen dissociation curve**. This would also have influenced the conversion of mixed venous oxygen content (CvO2) to mixed venous saturation (SvO2).

The percentage errors[3] for CvO2, SvO2, PvO2 and PvO2, the latter corrected for temperature and pH, were 24.2, 24.0, 26.3 and 12.0% respectively. CvO2, SvO2 and "uncorrected" PvO2 are equally far from the actual values. The percentage error for "corrected PvO2" is less than that for the other parameters. If the fixed position of the oxygen dissociation curve in the look-up table was indeed the problem, then the percentage error for CvO2 would have been lower than that for SvO2 and PvO2, which is not the case.

[3]Percentage error (the difference between predicted and actual values) informs how close or far one is from the actual answer.

On the other hand, the relationship between measured and estimated parameters can be interrogated by studying the coefficient of determination (r^2)[4] between parameters. The coefficients of determination for mixed venous oxygen content and saturation are 0.7 and 0.2 respectively. The strong and weak relationships between CvO2 and SvO2 suggest the fixed position of the oxygen dissociation curve in the look-up table might well be a problem.

Other non-invasive attempts to determine mixed venous oxygen saturation had the following results.

Regional cerebral oximetry via NIRS ($P<0.0001$), skeletal muscle tissue oxygenation (StO2) in patients with severe left heart failure without additional severe sepsis or septic shock ($P = 0.002$) and the trans-tracheal mixed venous oxygen saturation ($P < 0.05$) correlates with SvO2 obtained via invasive monitoring (PAC).

With **NIRS** however the wide limits of agreement imply that it might not be accurate to predict absolute values of SvO2 based solely on the non invasive measurement of regional cerebral oximetry (rSO2). Bland-Altman analysis showed a bias of +3.3% and a precision of 16.6% for rSO2 (regional cerebral oximetry) as a predictor of SvO2 for all patients. Even though **StO2** (skeletal muscle tissue oxygenation) correlates with SvO2, StO2 overestimated SvO2 (bias -2.3%, precision 4.6%). For **trans-tracheal mixed venous oxygen saturation** the mean +/- 2 SD difference between trans-tracheal and mixed venous oxygen saturation was 0.12% - 3.97% on the Bland-Altman graph. This imply that SvO2 can be monitored continuously and accurately by trans-tracheal pulse oximetry.(3)

Skeletal muscle tissue oxygenation (**StO2**) in patients with severe left heart failure and additional severe sepsis or septic shock, and SvO2 derived from the values measured by the **NICO** monitor do not correlate with mixed venous oxygen saturation measured using the pulmonary artery catheter. For NICO

[4]The coefficient of determination (r^2) describes the relationship between two variables, the higher the value the stronger the relationship

monitor derived SvO2, the bias +/- limits of agreement of the estimated SvO2 against measured SvO2 was -2.1% +/- 11.2%.

Looking at the above it is clear that the most accurate current non-invasive S vO2 monitor is trans-tracheal mixed venous oxygen saturation. SvO2 determined with the help of NIRS and skeletal muscle tissue oxygenation could potentially be used to indicate trends in SvO2.

Study limitations and strengths

Limitations

Potential or actual limitations of this method include the following:

1. It required tracheal intubation for accurate determination of oxygen consumption.
2. The position of the oxygen dissociation curve in the look-up table is “fixed" and would be affected by any factor affecting the P50 (position of the oxygen dissociation curve). These factors include temperature, carbon dioxide partial pressures, pH, carbon monoxide concentrations, and transfusion of stored bank blood.[50]
3. It required input of arterial oxygen content, a value that is not easily derived from non-invasive methods.
4. The oxygen-binding capacity of haemoglobin (Hoefts constant) of 1.39 ml oxygen per millilitre of blood was assumed. This value is the theoretical maximum; values between 1.34 to 1.39 have been suggested to be correct in clinical practice. We do not believe this to be of great

significance as a constant value was used. It may, however, account for a constant offset between invasive and non-invasive values.

5. The cost of lithium dilution technique exceeds that of the use of a pulmonary artery catheter by approximately a factor of 2.
6. The method requires a computer, haemoglobin concentration and a look up table to translate mixed venous oxygen content into saturation and partial pressures, values that are more understandable to clinicians.
7. Should errors occur in one or more measurements, the calculated mixed venous oxygen content will be incorrect.

Advantages

Potential advantages of this study include determining whether minimally-invasive determinations of venous oxygenation are indeed accurate and valid. If so, it could represent a major advance in minimally invasive monitoring.

Oxygen consumption measured by indirect calorimetry exceeds that calculated using VO2-Fick by about 30%. This is because intra-pulmonary oxygen consumption accounts for between 20 to 32% of total body oxygen consumption and VO2-Fick excludes this variable.[13] Therefore, indirect calorimetry determination of oxygen consumption is more accurate and probably preferable.

Conclusion

The hypothesis- the parameters of mixed venous oxygenation will not differ whether determined using minimally invasive techniques, or if measured using a pulmonary artery catheter, is thus rejected.

The hypothesis that less invasive and PAC thermodilution methods of calculating **cardiac output** produce similar results, is accepted.

The hypothesis that less invasive and reverse Fick methods of determining **oxygen consumption** produce similar results is rejected.

Circulatory efficiency could not be accurately predicted by minimally invasive methods of determining cardiac output and non-invasive methods of measuring oxygen consumption. Therefore, the parameters of **mixed venous oxygenation** will differ whether calculated using minimally invasive techniques or if measured from the pulmonary artery catheter.

Areas of future research

This study raises some interesting questions:

1. Why is oxygen consumption measured by indirect calorimetry not, in practice, accurate in measuring oxygen consumption? What are the factors that influence this technique the most and how can they be avoided?
2. What is the effect of vasopressors (changing systemic vascular resistance) and other drug infusions on the accuracy of LiDCO® determined cardiac output.
3. What is the accuracy of different minimally invasive cardiac output measurement techniques during and after hemodynamic changes?
4. It would be interesting to repeat this study using slightly different methodology that may remove the discontinuous time factors involved in this study:

a. Utilize continuous cardiac output and mixed venous saturation using a modified PAC for the “invasive" technique.
b. Utilize trans-pulmonary thermodilution techniques and direct Fick oxygen consumption but only after improving the accuracy with the latter.

Appendices

Appendix A A description of the non-invasive metabolic monitor for oxygen consumption: M-COVX™

Appendix B A description of the LiDCO™plus cardiac output monitor

Appendix C Consent and information documents

Appendix D Budget

Appendix E Data forms

Appendix F Spreadsheet to determine partial pressures of oxygen and saturation from content for a particular haemoglobin concentration

Appendix G Note on LiDCO cardiac output measurements

Appendix A

Details of the method whereby the General Electric M-COVX™ respiratory module calculates oxygen consumption.

Measurement of oxygen consumption is controversial because of technical measurement problems. The 'gold standard' for measuring oxygen consumption is a water-sealed spirometer, it is however impractical to use in the operating room or intensive care unit.

An alternative to the gas-exchange measurements mentioned above is calculation using the reverse Fick method. The reverse Fick method calculates oxygen consumption from cardiac output and arterial-mixed venous oxygen content difference. (These values are obtained with pulmonary artery catheters and arterial catheters.)

The current method of choice used clinically to obtain oxygen consumption in the operating room and intensive care unit is indirect calorimetry.[30-32]Currently the most acceptable system is a gas-exchange method called Deltatrac™. This came into clinical use in the mid- to late 1980's and is considered the gold standard[72]for clinical determination of oxygen consumption.[48]

A similar device to measure oxygen consumption by indirect calorimetery, which we used in this study, is the non-invasive metabolic monitor M-C OVX™. This device relates flow measurements to measurements of inspired and expired gas composition by matching the two waveforms thereby allowing continuous, breath-by-breath monitoring of an intubated patient's oxygen uptake and carbon dioxide production.[33-35] This metabolic monitoring device removes the need to measure both inspired and expired volumes by using the Haldane transformation. It assumes that inert gases, mostly nitrogen, are in the steady state. This enables multiple substitutions into the physiological equations, thereby removing

one of the volume measurements required.[73]

The M-COVX™ is a module for monitoring respiratory gas exchange and pulmonary mechanics. Albeit breath-by-breath measurements are made, the results of oxygen consumption, carbon dioxide production, energy expenditure and respiratory quotient calculation are averaged and updated every 60 seconds.

The M-COVX™ module comprises both a gas analyser and a spirometer. It uses paramagnetic oxygen sensors to measure oxygen concentrations, and infrared sensors to measure carbon dioxide concentrations.[74] Measurements are based on the difference between the amount of oxygen taken into the body and the amount exhaled.[73]A specialised commercially available "D-Lite+" sensor located at the patient's endotracheal tube measures flows. Sophisticated algorithms are employed to compensate for time delays and distortion of gas concentrations. The waveforms are reconstructed breath-by-breath and made to coincide so that the equation below can be solved.

$$VO_2 = \int_{insp} fO_2.TV - \int_{expir} fO_2.TV$$

Where TV = tidal volume

To obtain the oxygen consumption of a patient, the inhaled and exhaled amounts of oxygen are measured and the amount exhaled is then subtracted from the amount inhaled. Using the inspiratory(i) and expiratory(e) minute volumes (MV) this equations can be written as $VO_2 = FiO_2.MVi - FeO_2.MVe$

To make these results less sensitive to error in volume measurement the Haldane transformation is applied. This assumes that the patient is not taking up or excreting nitrogen.

$fiN_2.MVi = feN_2.Mve$, thus $MVi = feN_2.Mve/fiN_2$

Oxygen consumption can then be calculated using inspiratory minute volume (MVi)

$VO_2 = (fiO_2 - fhaldane.FeO_2)MVi$
$Fhaldane = fiN_2/feN_2 = 1 – fiO_2 – fiCO_2/1 – feO_2 – feCO_2$

Therefore:
$VO_2 = MVi(fiO_2 - (1 – fiO_2 – fiCO_2)/(1 – feO_2 – feCO_2)\ X\ feO_2)$ [19]

By deriving oxygen consumption from inspired volumes only, the measurements are less affected by leaks and incorrect assumptions about exhaled air temperature and humidity.[74]

Potential sources of error during continuous oxygen consumption measurement with the M-COVX™ has been investigated.[48] The main findings were that this monitor is reliable except when tidal volume measurement was inaccurate, which was most likely to be related to heated water bath humidification. This resulted from water condensation increasing flow resistance in the pneumotachograph. Using heat-and moisture-exchange filters avoids the need for heated water bath humidification in the intensive care unit. The M-COVX™ metabolic module is suitable for long periods of continuous oxygen consumption measurement in mechanically ventilated patients.[48]

The manufacturers quote the accuracy of the M-COVX™ module as being best with a FiO2 of less than 0.65, respiratory rates less than 35breath/min and normal airway pressures.[48, 58] This is because this module relies on tidal volume measurement for oxygen consumption calculation. The pneumotachograph derives the tidal volume from the pressure difference across a fixed orifice.[75] Increased resistance in the

tubing will increase the pressure difference and therefore overestimate the tidal volume. On the other hand, leaks in the system will lead to an underestimation of tidal volume.[48]

Given the ease with which the M-COVX™ metabolic monitor can be incorporated into existing anaesthetic monitoring systems, the fact that this method allows continuous measurement of gas exchange and its accuracy in measuring oxygen uptake, the M-COVX™ module is an attractive addition to existing perioperative monitoring.[33-36, 76, 77]

Appendix B

Description of the LiDCO™plus Hemodynamic Monitor

We used the LiDCO™plus Hemodynamic Monitor as a minimally/non-invasive technique to measure continuous cardiac output. It consists of the LiDCO™ & PulseCO™ systems and it provides a real time and comprehensive assessment of a patient's hemodynamic status.

The LiDCO™ System is a bolus indicator dilution method of measuring cardiac output (and intra-thoracic blood volume) and it is used to calibrate the PulseCO™ software. The bolus indicator dilution method of measuring cardiac output was first described by Henriques and developed by Hamilton et al in 1932.[46] This became widely adopted, the original technique using indocyanine green (ICG) as the marker. However, this technique required frequent blood sampling and manual analysis of the dilution curve, it proved to be technically difficult and time consuming. Lithium as an indicator of cardiac output was first described in 1993[78] and has since been extensively validated.[78]

A small dose of lithium chloride is injected via a central or peripheral venous line; the resulting arterial lithium concentration-time curve is recorded by withdrawing blood past a lithium sensor attached to the patient's existing arterial line. The monitor then calculates the cardiac output from the area of the primary dilution curve. The mean transit time of the lithium is derived for calculation of the intrathoracic blood volume. The method of using bolus indicator dilution to measure volume was described by Stewart[33-35] and the method of intrathoracic blood volume calculation is simply ITBV=C0xMTt. MTt is the mean transit time of the lithium indicator from injection to detection, ITBV is the intra-thoracic blood volume and CO is cardiac output.

The voltage across the sensor membrane is related via the Nernst equation

to the plasma [Li+.] A correction is applied for plasma sodium concentration because in the absence of lithium the baseline voltage is determined by the sodium concentration. The voltage is measured using an amplifier optically isolated from the patient. Indicator dilution curves recorded in arterial blood consist of primary and secondary curves due to the initial circulation and then re-circulation of the indicator. Cardiac output is calculated as:

Cardiac Output = (Lithium Dose x 60)/(Area x (1-PCV))

Where
Lithium dose is in mmol;
Area is the integral of the primary curve (mM.s);
PCV is packed cell volume which may be calculated as haemoglobin concentration (g/dl) / 34.Thislatter correction is needed because lithium is distributed only in plasma and not into the red or white cells on the first pass to the arterial circulation.

The PulseCO™ System calculates continuous beat-to-beat cardiac output by analysis of the arterial blood pressure trace following calibration with an absolute LiDCO cardiac output value.

The analogue arterial blood pressure trace from the conventional blood pressure monitor undergoes a three-step transformation

Step 1. Arterial pressure transformation into a volume-time waveform
Step 2. Deriving nominal stroke volume and heartbeat duration
Step 3. Actual stroke volume via calibration with an absolute cardiac output value (LiDCOplus brochure)

The concept of estimating cardiac output from the arterial pressure waveform has been extensively researched, the original researcher published by Erlanger and Hooker in 1904.[40]

It has also been shown that recalibration is unnecessary for at least eight hours[41][45, 46, 79, 80] and more recently for 24 hours.[49] The PulseCO software calculates the pulse power and derived stroke volume from the arterial waveform. PulseCO remains accurate and reliable over a wide range of hemodynamic states in post operative and intensive care settings.[41] According to above authors the LiDCOplus serves as a reliable alternative to continuous cardiac output monitoring with the pulmonary artery catheter.

In terms of accuracy, clinical studies have demonstrated that the LiDCO™ System method is at least as accurate as thermodilution over a wide range of cardiac outputs and in patients with varying cardiac outputs.[40, 42, 44-46] Some studies[47] indicated that LiDCO had a higher precision compared with conventional bolus thermodilution cardiac output. The signal to noise ratio and hence accuracy for lithium is better than that seen with thermodilution - due to the fact that the lithium dose can be scaled to the size and cardiac output of the patient. Thermal noise from fluid infusion, respiration and patient warming has little, if any, effect on the lithium curve. The precision of the LiDCO System method implies that only one lithium injection is supposed to be required to accurately determine the cardiac output.

The dose of lithium marker needed (0.15 – 0.3 mmol for an average adult) is very small and has no known pharmacological effects.[41, 45]

Multiple dosages of Lithium have been extensively investigated and the safety profile is well established. The pharmacokinetics of intravenous lithium chloride in man (and animals) has been documented.[43] Lithium chloride has been used extensively in medicine for prophylactic and therapeutic treatment of unipolar and bipolar manic-depressive disorders.[81-83] The lithium chloride is distributed throughout the total body water and excreted almost entirely by the kidneys.

The half-life of lithium chloride in humans is 19.8 - 41.3 hrs.[44] The

recommended maximum total dose for a Lithium indicator dilution would have to be exceeded many times before toxic levels are reached. In fact, a single lithium chloride LiDCO indicator dilution determination at 0.3mmol is the equivalent to a steady state plasma lithium concentration of 1/240th of the therapeutic level. Lithium has been used for the measurement of cardiac output in thousands of patients over many years without a single side effect being reported.

In order to use the technology, a monitor (LiDCO™plus), single patient use lithium dilution sensor and associated disposables are required. It is designed to work with any of the commonly used arterial catheter systems. The indicator dilution calibration method does not require the use of special catheters, introducer trays or a subsequent x-ray for catheter position verification. Savings can usually be realized against the costs associated with the use of more invasive technologies, and the elimination of the potential co morbidities associated with pulmonary artery catheter insertion.

The LiDCO™plus Hemodynamic Monitor is suitable for patients who have arterial and venous catheters (peripheral or central) inserted and who require hemodynamic monitoring.

Patients undergoing treatment with lithium salts, patients who are less than 40kg in weight and patients in the first trimester of pregnancy are contraindicated for calibration with the lithium chloride indicator.

Performance of the continuous waveform analysis PulseCO software may be compromised in patients with severe peripheral arterial vasoconstriction, those undergoing treatment with aortic balloon pumps and in the case of aortic valve regurgitation.

The LiDCO™plus system have US Food and Drug Administration approval and has been marketed since July 2001. Over 80 key institutions in the USA and

over 50 institutions in the UK are routinely using the LiDCO technology.[37]

Appendix C:

Consent and patient information form

TITLE OF THE RESEARCH PROJECT:

Comparison of minimally and more invasive methods of determining circulatory efficiency

ETHICS COMMITTEE REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: DR M Smit supervised by Prof A Levin

ADDRESS: Department of Anaesthesiology and Critical Care, Stellenbosch University, Tygerberg Hospital, Fransie Van Zyl Avenue, Bellville, 7530

TELEPHONE NUMBERS: +0820849521996/ +2721 9385142

e mail:smitmarli@yahoo.com

Patient name: Hospital ID number Place patient sticker here if available

INTRODUCTION TO A RESEARCH PROJECT: YOUR RIGHTS AND RESPONSIBILITIES

1. You are being invited to take part in a research project.

2. Please take some time to read the information presented here, which will explain the details about this project.

3. 4. It is very important that you are clearly understand what this research entails and how you could be involved.

4. Please ask the doctor any questions about any part of this project that you do not fully understand.

5. Your participation is **entirely voluntary** and you are free to decline to participate. If you do decline, the decision will not affect you negatively in any way whatsoever.

6. You are free to withdraw from the study at any point, even if you initially agreed to participate.

7. This study has been approved by the **Committee for Human Research at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the **International Declaration of Helsinki**, **South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research**.

WHAT IS THIS RESEARCH PROJECT ALL ABOUT?

1. This research wishes to see if we can predict how good (effective) your circulation is using a minimally an invasive method during and after your surgery.
2. The usual method is to insert a thin pipe (catheter) into a blood vessel in the lung, a procedure we frequently perform during cardiac and other surgery. Via this catheter, we will draw half to one millilitre (less than one fifth of a teaspoon) of blood approximately 12 times during your stay in the theatre and intensive care unit.
3. The non invasive method involves attaching a monitor to your airway, a technique that is ordinarily done during anaesthesia. This will measure how much oxygen your body consumes.
4. The other aspect is to attach a detector to your intra-arterial catheter. This is a new but well tested and safe device that can measure how much blood your heart is putting out. To calibrate the device, we will inject a very small dose of a marker called lithium. The dose of lithium marker needed is very small and has no known side effects
5. We wish to compare the two methods.

WHY HAVE YOU BEEN INVITED TO PARTICIPATE?

You have been invited to participate because you are scheduled to undergo cardiac surgery during which certain catheters (pipes) are intended to be placed.

OTHER RELEVANT INFORMATION

- Your participation will only be for the period you are in theatre and the first day or two after surgery in the ICU.
- We will chart the observations.
- We are currently working on the number of patients to be involved in this study. We will look at the data collected from the first 10 patients have been done and estimate how many subjects need to be enrolled in the study.

ARE THERE ANY RISKS INVOLVED IN TAKING PART IN THIS PROJECT?

1. We believe that this may be more accurate and non-invasive method of determining how effective your circulation is.

2. We do not foresee risks in this trial as the newer method is potentially more accurate and is a well recognised technique used thousands of times before.
3. We intend to practice very much as we ordinarily do as to break usual practice would invalidate any conclusions we would wish to draw.

WHAT WILL HAPPEN IN THE UNLIKELY EVENT OF SOME FORM OF INJURY OCCURRING AS A DIRECT RESULT OF YOUR TAKING PART IN THIS PROJECT?

It is highly unlikely that injury can occur as a direct result of your taking part in this research project.

It is purely and observational study and we do not wish to make any conclusions during the time you are in theatre using these monitors. The data collected will be analysed afterwards.

WHO WILL HAVE ACCESS TO YOUR MEDICAL RECORDS?

1. The information collected will be treated as confidential.
2. If it is used in a publication, your identity will remain anonymous.
3. Only the investigators involved in this project will have access to your information.

WILL YOU BE PAID TO PARTICIPATE IN THE STUDY AND WILL BE ANY COSTS INVOLVED?

1. You will not be paid to take part in the study.

2. There will be no costs involved for you, if you do take part.

IF YOU HAVE ANY QUESTIONS YOU CAN CONTACT:

1. Dr Marli Smit, the study doctor at the contact details above.

2. The Committee for Human Research at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

DECLARATION BY PATIENT

By signing below, I, _____ agree to take part in a research study entitled "**Comparison of minimally and more invasive methods of determining circulatory efficiency:**"

I declare that:

1. I have read or had read to me this information and consent form.
2. It is written in a language with which I am fluent and comfortable.
3. I have had a chance to ask questions and all my questions have been adequately answered.
4. I understand that taking part in this study is **voluntary** and I have not been pressurized to take part.
5. I may choose to leave the study at any time and will not be penalized or prejudiced in any way.

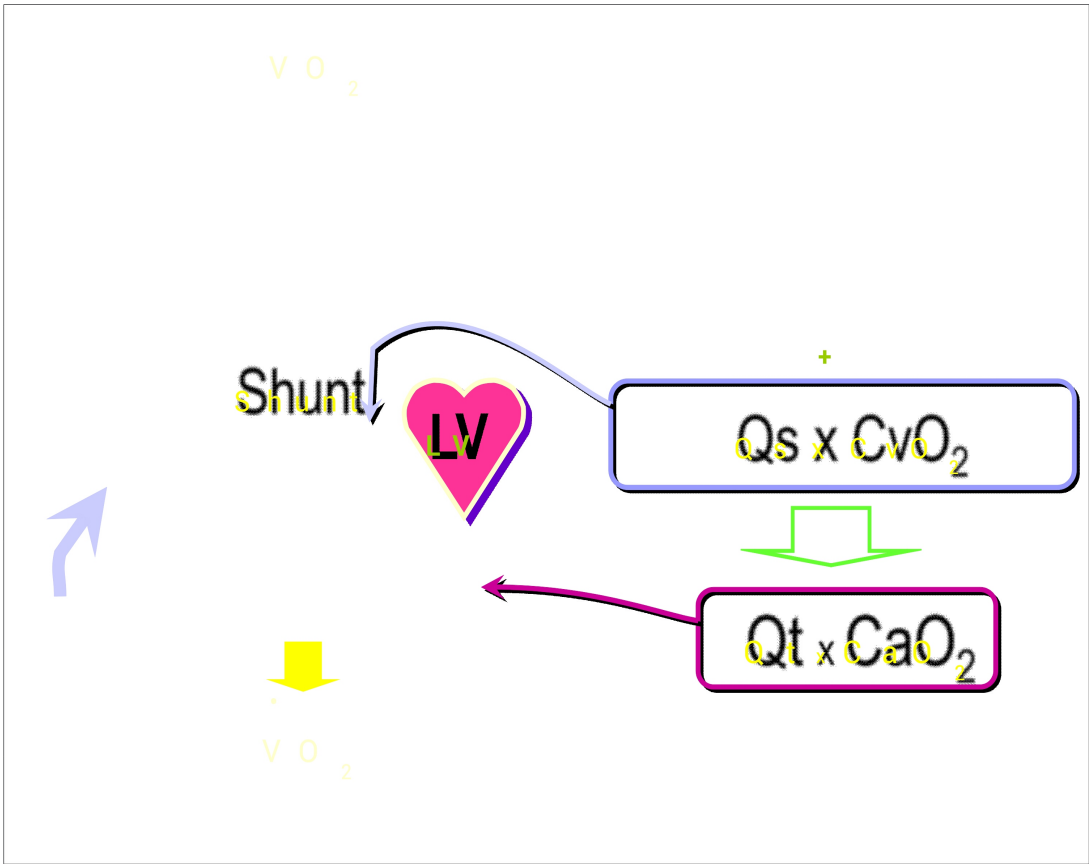
Signed at (place) **_TYGERBERG HOSPITAL____** on (date) _____

Signature of participant _____

Signature of witness _____

Appendix D: Budget

Personnel compensation **- Principal investigator**	**None**
- Project coordinator	**None**
- Data typist	**Departmental secretary**
Travel	**None**
Consulting services **- statistical services**	**Prof JF Coetzee: no charge**
Equipment **- Computer**	**Exists**
- LiDCO™	**Exists**
- M-COVX™	**Exists**
- Pulmonary artery catheter	**Per definition, routine clinical use**
Lithium	**R1800 per case**
Diverse **- Printing**	**Departmental funds**
- Internet	**Departmental funds**
Total	**R 1800 per case**



Description of study techniques

by rewriting the Fick equation

$$VO_2 = Qt(CaO_2 - CvO_2)$$

Classic invasive technique:

Cardiac output, CvO2 and CaO2 will be measured. VO2 is calculated

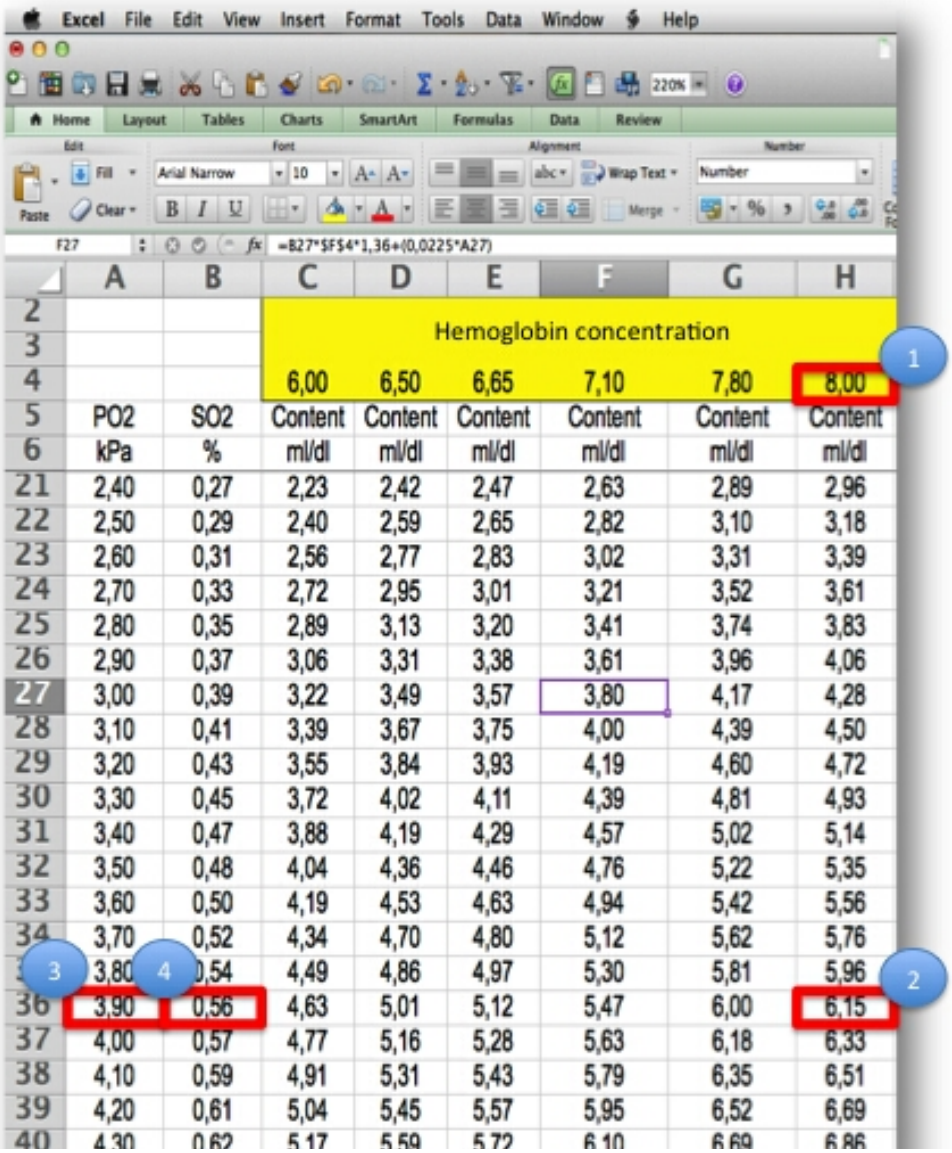
$$CvO_2 = CaO_2 - [VO_2/Qt]$$

Minimally invasive technique:

VO2, cardiac output and CaO2 will be measured. CvO2 will be calculated

H. Scharf: Cardiopulmonary Physiology in Critical Care. 1992

Appendix F
Screenshot of part of oxygen dissociationspread



	A	B	C	D	E	F	G	H
2			Hemoglobin concentration					
3								
4			6,00	6,50	6,65	7,10	7,80	8,00
5	PO2	SO2	Content	Content	Content	Content	Content	Content
6	kPa	%	ml/dl	ml/dl	ml/dl	ml/dl	ml/dl	ml/dl
21	2,40	0,27	2,23	2,42	2,47	2,63	2,89	2,96
22	2,50	0,29	2,40	2,59	2,65	2,82	3,10	3,18
23	2,60	0,31	2,56	2,77	2,83	3,02	3,31	3,39
24	2,70	0,33	2,72	2,95	3,01	3,21	3,52	3,61
25	2,80	0,35	2,89	3,13	3,20	3,41	3,74	3,83
26	2,90	0,37	3,06	3,31	3,38	3,61	3,96	4,06
27	3,00	0,39	3,22	3,49	3,57	3,80	4,17	4,28
28	3,10	0,41	3,39	3,67	3,75	4,00	4,39	4,50
29	3,20	0,43	3,55	3,84	3,93	4,19	4,60	4,72
30	3,30	0,45	3,72	4,02	4,11	4,39	4,81	4,93
31	3,40	0,47	3,88	4,19	4,29	4,57	5,02	5,14
32	3,50	0,48	4,04	4,36	4,46	4,76	5,22	5,35
33	3,60	0,50	4,19	4,53	4,63	4,94	5,42	5,56
34	3,70	0,52	4,34	4,70	4,80	5,12	5,62	5,76
35	3,80	0,54	4,49	4,86	4,97	5,30	5,81	5,96
36	3,90	0,56	4,63	5,01	5,12	5,47	6,00	6,15
37	4,00	0,57	4,77	5,16	5,28	5,63	6,18	6,33
38	4,10	0,59	4,91	5,31	5,43	5,79	6,35	6,51
39	4,20	0,61	5,04	5,45	5,57	5,95	6,52	6,69
40	4,30	0,62	5,17	5,59	5,72	6,10	6,69	6,86

sheet

Formula of oxygen dissociation curve used for deriving mixed venous oxygen saturation from mixed venous oxygen content:

$$Saturation \quad {}_{P}O_2^3 + [2.667 \times {}_{P}O_2]$$

~~$${}_{P}O_2^3 + [2.667 \times {}_{P}O_2] + 55.47$$~~

Appendix G
Note on LiDCO cardiac output measurements

Although the correlation between PAC and LiDCO derived cardiac outputs was good, we felt that it is worth noting some of the practical difficulties when using the LiDCO.

Major problems were at times experienced during LiDCO calibration. In one patient we couldn't get an acceptable calibration and had to terminate attempts because we were running the risk of exceeding the recommended dose of lithium. In interpreting the correlation between cardiac output measured by PAC and LiDCO one has to keep in mind that we purposely recalibrated during known or expected hemodynamic changes.

We also experienced that diathermy and surgical factors (surgeon touching the heart) interfered with system calibration. The sensor responsible for calibration became defective on two separate occasions and had to be replaced. There were also two patients that we had to exclude from our study secondary to known reasons that made LiDCO measurements unreliable. One patient had aortic incompetence and another had to be treated with an aortic balloon pump after bypass.

The blood loss (approximately 250 to 400 milliliters of blood) that always accompanies the LiDCO calibration process was also troubling.

References

1. Braunwald, E., 50th anniversary historical article. Myocardial oxygen consumption: the quest for its determinants and some clinical fallout. J Am.Coll.Cardiol., 2000. **35**(5 Suppl B): p. 45B-48B.

2. Tweddell, J.S., et al., Mixed venous oxygen saturation monitoring after stage 1 palliation for hypoplastic left heart syndrome. Ann Thorac Surg, 2007. **84**(4): p. 1301-10; discussion 1310-1.

3. Edwards, J.D. and R.M. Mayall, Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. Crit Care Med., 1998. **26**(8): p. 1356-1360.

4. Wei, W., et al., A pilot study of continuous transtracheal mixed venous oxygen saturation monitoring. Anesth Analg., 2005. **101**(2): p. 440-3, table.

5. Steel, A. and D. Bihari, Pulmonary artery catheterisation--a problem swept under the carpet? Crit Care Resusc, 2000. **2**(2): p. 146-9.

6. Kotake, Y., et al., Can mixed venous hemoglobin oxygen saturation be estimated using a NICO monitor? Anesth Analg., 2009. **109**(1): p. 119-123.

7. Tortoriello, T.A., et al., A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth, 2005. **15**(6): p. 495-503.

8. Podbregar, M. and H. Mozina, Skeletal muscle oxygen saturation does not estimate mixed venous oxygen saturation in patients with severe left heart failure and additional severe sepsis or septic shock. Crit

Care., 2007. **11**(1): p. R6.

9. Puyana, J.C. and M.R. Pinsky, Searching for non-invasive markers of tissue hypoxia. Crit Care., 2007. **11**(1): p. 116.

10. Varpula, M., et al., Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. Intensive Care Med., 2006. **32**(9): p. 1336-1343.

11. Pieri, M., et al., [Comparison of bench central and mixed pulmonary venous oxygen saturation in critically ill postsurgical patients]. Minerva Anestesiol., 1995. **61**(7-8): p. 285-291.

12. Dueck, M.H., et al., Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. Anesthesiology., 2005. **103**(2): p. 249-257.

13. Oudemans-van Straaten, H.M., et al., Oxygen consumption after cardiopulmonary bypass--implications of different measuring methods. Intensive Care Med., 1993. **19**(2): p. 105-110.

14. Edwards, J.D., Oxygen transport in cardiogenic and septic shock. Crit Care Med., 1991. **19**(5): p. 658-663.

15. Rivers, E.P., D.S. Ander, and D. Powell, Central venous oxygen saturation monitoring in the critically ill patient. Curr.Opin.Crit Care., 2001. **7**(3): p. 204-211.

16. Robin, E., et al., Clinical relevance of data from the pulmonary artery catheter. Crit Care, 2006. **10 Suppl 3**: p. S3.

17. Birman, H., et al., Continuous monitoring of mixed venous oxygen saturation in hemodynamically unstable patients. Chest., 1984. **86**(5):

p. 753-756.

18. Powelson, J.A., et al., Continuous monitoring of mixed venous oxygen saturation during aortic operations. Crit Care Med., 1992. **20**(3): p. 332-336.

19. Polonen, P., et al., A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg., 2000. **90**(5): p. 1052-1059.

20. de la Rocha, A.G., et al., Importance of mixed venous oxygen saturation in the care of critically ill patients. Can J Surg., 1978. **21**(3): p. 227-229.

21. Krafft, P., et al., Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. Chest., 1993. **103**(3): p. 900-906.

22. O'Connor, T.A. and R.T. Hall, Mixed venous oxygenation in critically ill neonates. Crit Care Med., 1994. **22**(2): p. 343-346.

23. Conacher, I.D. and M.L. Paes, Mixed venous oxygen saturation during lung transplantation. J Cardiothorac.Vasc.Anesth., 1994. **8**(6): p. 671-674.

24. Ahrens, T., Continuous mixed venous (SvO2) monitoring. Too expensive or indispensible? Crit Care Nurs.Clin.North Am., 1999. **11**(1): p. 33-48.

25. McGee, D.C. and M.K. Gould, Preventing complications of central venous catheterization. N.Engl.J Med, 2003. **348**(12): p. 1123-1133.

26. Roizen, M., Practice guidelines for pulmonary artery catheterization. A report by the American Society of Anesthesiologists Task Force on

Pulmonary Artery Catheterization. Anesthesiology, 1993. **78**(2): p. 380-394.

27. Roizen, M., Practice guidelines for pulmonary artery catheterization: an updated report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology, 2003. **99** (4): p. 988-1014.

28. Lee, J., et al., Central venous oxygen saturation in shock: a study in man. Anesthesiology., 1972. **36**(5): p. 472-478.

29. Scheinman, M.M., M.A. Brown, and E. Rapaport, Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation., 1969. **40**(2): p. 165-172.

30. Epstein, C.D., et al., Comparison of methods of measurements of oxygen consumption in mechanically ventilated patients with multiple trauma: the Fick method versus indirect calorimetry. Crit Care Med., 2000. **28**(5): p. 1363-1369.

31. Nunn, J.F., Pulmonary oxygen consumption. Intensive Care Med., 1996. **22**(4): p. 275-276.

32. deBoisblanc, B.P., E. McClarity, and K. Lord, Oxygen consumption in the intensive care unit: indirect calorimetry is the way to go, but where? Crit Care Med., 1998. **26**(7): p. 1153-1154.

33. Stuart-Andrews, C., et al., Non-invasive metabolic monitoring of patients under anaesthesia by continuous indirect calorimetry--an in vivo trial of a new method. Br J Anaesth, 2007. **98**(1): p. 45-52.

34. Stuart-Andrews, C.R., et al., In vivo validation of the M-COVX metabolic monitor in patients under anaesthesia. Anaesth Intensive Care., 2007.

35(3): p. 398-405.

35. Stuart-Andrews, C.R., et al., Laboratory validation of the M-COVX metabolic module in measurement of oxygen uptake. Anaesth Intensive Care., 2009. **37**(3): p. 399-406.

36. Steinhorn, D.M., et al., Modular indirect calorimeter suitable for long-term measurements in multipatient intensive care units. Crit Care Med., 1991. **19**(7): p. 963-972.

37. Pearse, R.M., K. Ikram, and J. Barry, Equipment review: an appraisal of the LiDCO plus method of measuring cardiac output. Crit Care., 2004. **8** (3): p. 190-195.

38. Nelson, L.D., The new pulmonary arterial catheters. Right ventricular ejection fraction and continuous cardiac output. Crit Care Clin., 1996. **12**(4): p. 795-818.

39. Godje, O., et al., Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. Crit Care Med, 2002. **30**(1): p. 52-8.

40. Erlanger and Hooker, An experimental Study of blood pressure and of pulse pressure in man. John Hopkins Hosp Rep 1904. **12**: p. 145-378.

41. Pittman, J., et al., Continuous cardiac output monitoring with pulse contour analysis: a comparison with lithium indicator dilution cardiac output measurement. Crit Care Med., 2005. **33**(9): p. 2015-2021.

42. al, J.e., The pharmacokinetics of intravenous lithium chloride in patients and normal volunteers. J. trace Elements Microprobe Technologies 2001. **19**.

43. M, J., et al. Comparison of cardiac output measurements using a

continuous arterial waveform analysis monitor (PulseCO) with an indicator dilution technique (LiDCO) in patients in intensive care. in ICCM 2001. Sydney.

44. Mason, D.J., et al., Assessment of lithium dilution cardiac output as a technique for measurement of cardiac output in dogs. Am.J Vet.Res., 2001. **62**(8): p. 1255-1261.

45. B, H.L., et al., Continuous Intraoperative Cardiac Output Determination with Arterial Pulse Wave Analysis (PulseCO™) is Valid and Precise. Anesth. Analg, 2002. **93**: p. SCA1-SCA112.

46. Hamilton, T.T., L.M. Huber, and M.E. Jessen, PulseCO: a less-invasive method to monitor cardiac output from arterial pressure after cardiac surgery. Ann.Thorac.Surg., 2002. **74**(4): p. S1408-S1412.

47. Kurita, T., et al., Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output. Br.J Anaesth., 1997. **79**(6): p. 770-775.

48. Donaldson, L., S. Dodds, and T.S. Walsh, Clinical evaluation of a continuous oxygen consumption monitor in mechanically ventilated patients. Anaesthesia., 2003. **58**(5): p. 455-460.

49. al, K.C.e., A comparison of two calibrated, continuous, arterial pressure waveform based measurements of cardiac output over 24 hours. Crit Care Med, 2005. **33**.

50. Aberman, A. and E. Hew, Clarification of the effects of changes in P50 on oxygen transport. Acute.Care., 1985. **11**(3-4): p. 216-221.

51. Marson, F., et al., Correlation between oxygen consumption calculated using Fick's method and measured with indirect calorimetry in

critically ill patients. Arq Bras Cardiol, 2004. **82**(1): p. 77-81, 72-6.

52. Bizouarn, P., Y. Blanloeil, and M. Pinaud, Comparison between oxygen consumption calculated by Fick's principle using a continuous thermodilution technique and measured by indirect calorimetry. Br J Anaesth, 1995. **75**(6): p. 719-23.

53. Bizouarn, P., et al., Oxygen consumption after cardiac surgery--a comparison between calculation by Fick's principle and measurement by indirect calorimetry. Intensive Care Med, 1992. **18**(4): p. 206-9.

54. Hofland, J., et al., Comparison of closed circuit and Fick-derived oxygen consumption in patients undergoing simultaneous aortocaval occlusion. Anaesthesia, 2003. **58**(4): p. 377-84.

55. Walsh, T.S., P. Hopton, and A. Lee, A comparison between the Fick method and indirect calorimetry for determining oxygen consumption in patients with fulminant hepatic failure. Crit Care Med, 1998. **26**(7): p. 1200-7.

56. Stock, M.C. and M.E. Ryan, Oxygen consumption calculated from the Fick equation has limited utility. Crit Care Med, 1996. **24**(1): p. 86-90.

57. McClave, S.A., et al., Achievement of steady state optimizes results when performing indirect calorimetry. JPEN J Parenter Enteral Nutr, 2003. **27**(1): p. 16-20.

58. McLellan, S., et al., Comparison between the Datex-Ohmeda M-COVX metabolic monitor and the Deltatrac II in mechanically ventilated patients. Intensive Care Med., 2002. **28**(7): p. 870-876.

59. Sander, M., et al., Pulse contour analysis after normothermic cardiopulmonary bypass in cardiac surgery patients. Crit Care, 2005. **9**

(6): p. R729-34.

60. Siranovic, M., et al., Constant cardiac output monitoring using the PiCCO and LiDCO methods versus PAK in septic patients: when to do calibration? Acta Clin Croat, 2011. **50**(2): p. 267-72.

61. Beattie, C., et al., The effect of anaesthesia and aortic clamping on cardiac output measurement using arterial pulse power analysis during aortic aneurysm repair. Anaesthesia, 2010. **65**(12): p. 1194-9.

62. Bein, B., et al., The reliability of pulse contour-derived cardiac output during hemorrhage and after vasopressor administration. Anesth Analg, 2007. **105**(1): p. 107-13.

63. Hamilton, M.A., M. Cecconi, and A. Rhodes, A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. Anesth Analg, 2011. **112**(6): p. 1392-402.

64. Cecconi, M., et al., Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies--with specific reference to the measurement of cardiac output. Crit Care, 2009. **13**(1): p. 201.

65. Reed, G.F., F. Lynn, and B.D. Meade, Use of coefficient of variation in assessing variability of quantitative assays. Clin Diagn Lab Immunol, 2002. **9**(6): p. 1235-9.

66. Hofer, C.K., M.T. Ganter, and A. Zollinger, What technique should I use to measure cardiac output? Curr Opin Crit Care, 2007. **13**(3): p. 308-17.

67. Nishikawa, T. and S. Dohi, Errors in the measurement of cardiac output by thermodilution. Can J Anaesth, 1993. **40**(2): p. 142-53.

68. Enomoto, N., S. Tachizawa, and K. Yamashita, [Anesthesia in surgery of pheochromocytoma. Combined use of Dibenzyline and Inderal]. Masui, 1966. **15**(12): p. 1253-9.

69. Sander, M., et al., Comparison of uncalibrated arterial waveform analysis in cardiac surgery patients with thermodilution cardiac output measurements. Crit Care, 2006. **10**(6): p. R164.

70. Pugsley, J. and A.B. Lerner, Cardiac output monitoring: is there a gold standard and how do the newer technologies compare? Semin Cardiothorac Vasc Anesth, 2010. **14**(4): p. 274-82.

71. Ambrisko, T.D., et al., Lithium dilution, pulse power analysis, and continuous thermodilution cardiac output measurements compared with bolus thermodilution in anaesthetized ponies. Br J Anaesth, 2012. **109**(6): p. 864-9.

72. Singer, P., et al., Comparison of metabolic monitors in critically ill, ventilated patients. Nutrition., 2006. **22**(11-12): p. 1077-1086.

73. PT, R.J.P., Validation of an indirect calorimeter to measure oxygen consumption in critically ill patients. Journal of critical care 1991. **6**.

74. Gradinac, S., et al., Improved cardiac function with glucose-insulin-potassium after aortocoronary bypass grafting. Ann Thorac Surg, 1989. **48**(4): p. 484-9.

75. Merilainen, P., H. Hanninen, and L. Tuomaala, A novel sensor for routine continuous spirometry of intubated patients. J Clin.Monit., 1993. **9**(5): p. 374-380.

76. Takala, J. and P. Meriläinen, Handbook of indirect calorimetry and Gas Exchange. Datex-Ohmeda.

77. Ronco, J.J. and P. P.T., Validation of an indirect calorimeter to measure oxygen consumption in critically ill patients. Journal of Critical Care, 1991. **6**: p. 36-41.

78. Linton, R.A., D.M. Band, and K.M. Haire, A new method of measuring cardiac output in man using lithium dilution. Br.J Anaesth., 1993. **71** (2): p. 262-266.

79. A, A., et al., Continuous intraoperative cardiac output determination with arterial pulse wave analysis (PulseCO™) is valid and precise, in Society of Cardiovascular Anesthesiologists Annual Meeting2002.

80. al, M.e. Perioperative hemodynamic beat-to-beat monitoring of cardiac output:the new PulseCO system. in American Soc. Of Anesthesiology, New Orleans, Oct., Abstracts. 2001. New Orleans.

81. Amidsen, Lithium. Schentag et al, Applied pharmacokinetics: principles of therapeutic drug monitoring. San Francisco: Therapeutics Inc 1980.

82. al, P.e., Lithium in the treatment of mood disorders. N Engl J Med, 1994. **331**.

83. Price, L.H. and G.R. Heninger, Lithium in the treatment of mood disorders. N.Engl.J Med., 1994. **331**(9): p. 591-598.