The effect of halothane, enflurane and isoflurane on the circulation

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Summary

This study, in open-chested dogs, sought to explore the relationship between whole-body oxygen delivery and oxygen consumption during anaesthesia, using increasing concentrations of halothane, enflurane and isoflurane. Results indicate that the cardiac index and oxygen delivery became critical at less than 1 MAC (minimal alveolar concentration of anaesthetic) for the three commonly used vapours. Halothane caused the least depression of contractility, but the stroke volume was reduced by the well-maintained afterload at 1 MAC. Enflurane and isoflurane were associated with more depression of contractility, but the cardiac output was maintained by an increase in heart rate in the case of isoflurane and reduced mean arterial pressure during the use of enflurane.

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Myocardial contractility represents the potential of the heart to do work under a given set of circumstances. However, the expression of this potential is modified by the heart rate (HR) afterload and preload. The anaesthesiologist is concerned with the maintenance of cellular oxygenation, and cardiac output (CO) therefore justifies more of his attention than myocardial contractility *per se*.

This study was undertaken to elucidate the effect of halothane, enflurane and isoflurane on myocardial contractility and the function of the heart as a pump with specific reference to the maintenance of cellular oxygenation.

Materials and methods

The study was approved by the Ethics Committee of the University of Stellenbosch Medical School and care of the animals was in accordance with national and institutional guidelines.

Thirty mongrel dogs, mean weight 24,7 kg (range 20,5 -29,2 kg), were used. Each anaesthetic agent was evaluated in 10 animals.

The animals were premedicated with intramuscular morphine 1,5 mg/kg and anaesthesia was induced with intravenous fentanyl 15 μg/kg and thiopentone 15 mg/kg. After endotracheal intubation the animals were mechanically ventilated with 40% oxygen and 60% nitrogen (fresh gas flow 3 l/min). The tidal volume was adjusted to maintain the partial arterial carbon dioxide pressure ($PaCO_2$) between 4,6 and 5,2 kPa. The anaesthetic gases were vaporised from calibrated vaporisers (halothane: Dragerwerk, Germany; enflurane and isoflurane: Cyprane, UK) and the end-tidal concentrations of the anaesthetic gases were monitored (Normac; Datex, Finland).

Normal saline was infused at a rate of 5 ml/kg/h and fentanyl 7 μg/kg/h was added to the infusion.

Temperature, which was monitored from the thermistor at the tip of the pulmonary artery catheter, was maintained between 36,5 and 37,3°C with the aid of an under-table heating system.

Through an incision in the neck a cannula was positioned in the aorta via the internal carotid artery and connected to a pressure transducer (Statham P23; Statham, Hato Rey — natural frequency 50,3 Hz). This was used to monitor blood pressure. A 7F pulmonary artery (PA) catheter (Edwards Laboratories, USA) was floated into the proximal PA. Five per cent dextrose at 0°C was manually injected into the PA catheter for the determination of CO by the thermodilution method (Mansfield 9530 Cardiac Output Computer, USA). The mean of three values is reported.

A left thoracotomy was performed and the heart suspended in a pericardial cradle. A 16G cannula was sutured into the left ventricle (LV) apex for determination of LV pressures (Pressure transducer: Statham P23; natural frequency 50,4 Hz). An 18G cannula was sutured into the proximal pulmonary artery to facilitate the withdrawal of mixed venous ($\bar{v}$) blood.

Two piezo-electric crystals were positioned in the LV subendocardium in the minor axis of the heart; segment length could then be measured with the aid of microsonometry (Schuessler and Ass, USA).[1] Change in length of the subendocardium and the LV pressure were combined on a storage oscilloscope (Textronix 5103N, USA) to give a continuous pressure-length (P-L) loop. Constant calibrations for the P-L loops on the oscilloscope were used throughout the experiments.

An occlusion balloon catheter (Fogerty size 8 - 14F; Edward Laboratories, USA) was positioned in the aorta to change the loading of the ventricle and thereby obtain the end-systolic P-L (E_{es}) relationship, which served as an index of contractility[2-5] (Fig. 1).

Calibrations of pressure transducers were done with a mercury manometer before and during the experiments. Record-

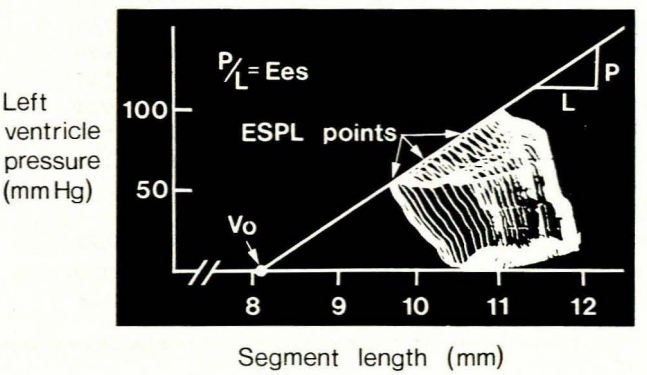

Fig. 1. The end-systolic pressure-length ratio (E_{es}) obtained by computer from afterload LV contractions. The slope of E_{es} is a load-independent index of myocardial contractility.

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ings were made at the end-expiratory phase and data were stored directly on floppy disk using a microcomputer with a mathematical microprocessor and an analogue to digital converter. Sampling was done at a rate of 200 Hz for 5 seconds. The HR was obtained from the R-R interval of the ECG.

Arterial and mixed venous blood was withdrawn into preheparinised, chilled syringes and kept in ice until the determination of blood gases, haemoglobin (Hb), Hb saturation and carboxyhaemoglobin (COHb) was performed (IL 282 Co Oximeter; IL 613 Blood Gas Analyzer; Instrumentation Laboratories, USA). The Severinghaus correction factors were applied for temperature, pH and $PaCO_2$.[6]

The primary measurements were applied to standard haemodynamic equations. Oxygen consumption was calculated as follows:

$$\dot{V}O_2 = CO. (CaO_2 - C\bar{v}O_2), \text{ where}$$

$CaO_2 = 0{,}0139 \times Hb \times Hb$ saturation $+ 0{,}0031 \times PaO_2$ and $C\bar{v}O_2 = 0{,}0139 \times Hb \times Hb$ saturation $+ 0{,}0031 \times P\bar{v}O_2$. COHb was taken into account in the calculations for CaO_2 and $C\bar{v}O_2$.

The ratio of supply and demand was expressed as the coefficient of oxygen delivery (COD) = $CaO_2/(CaO_2 - C\bar{v}O_2)$.[7]

Data were subjected to multiple analysis of variance for comparison between the lowest concentration used for each anaesthetic gas (i.e. 'controls') and each subsequent measurement. $P < 0{,}05$ was considered a significant difference.

Experimental design

The anaesthetic gas concentration was increased in steps as indicated. Twenty-five minutes were allowed for stabilisation at each new concentration before measurements were taken. Between steps the calibrations of pressures and blood gases were checked and corrections were made when necessary.

The anaesthetic gas concentrations evaluated were as follows: halothane — 0,5%, 0,7%, 1,0%, 1,5%, 2,0%; enflurane —0,77%, 1,2%, 1,68%, 2,13%, 2,57%; isoflurane — 0,77%, 1,13%, 1,52%, 1,90%, 2,13%.

These concentrations were obtained by a predetermined stepwise increase in the dial setting of the various vaporisers, but the final end-expiration concentration (given above) represents the actual values as obtained from the end-tidal anaesthetic gas determination. Minimal alveolar concentration (MAC) of anaesthetic values applied to data from this study are similar to those reported by Joas *et al.*[8]

To obtain the end-systolic pressure-length (ESPL) relationship, the intra-aortic balloon was inflated over 5 - 10 beats. The increasing end-systolic pressure and length points were registered and the microcomputer calculated the maximum ESPL ratio for each beat. Linear regression (least-squares method) was performed on the data and the ESPL ratio, or E_{es}, was calculated.

Results

Values in Tables I - III are the means (± SE) for the number of experiments as indicated.

Because the haemoglobin concentration, PaO_2 and SaO_2 did not decrease in any of the studies, it is accepted that CaO_2 remained constant during the study.

Halothane (Table I)

There was a decrease in the cardiac index (CI) as the halothane concentration was increased above 1,2 MAC. This was caused by a decrease in myocardial contractility (E_{es}) once the halothane concentration was 0,89 MAC and over. Preload remained constant and the mean arterial pressure (MAP) decreased significantly when the halothane was administered in concentrations of 1,20 MAC. The $\dot{V}O_2$ did not vary and because of the decrease in CI, the $(a - \bar{v})\ DO_2$ increased significantly if 1,72 MAC and more halothane was administered.

Enflurane (Table II)

The CI decreased significantly when enflurane was given in concentrations higher than 0,97 MAC. This decrease was caused by a decrease in myocardial contractility (E_{es}). The $\dot{V}O_2$

TABLE I. CARDIOVASCULAR EFFECTS OF INCREASING CONCENTRATIONS OF HALOTHANE (MEAN ± SE FOR ANIMALS)

	Halothane (MAC)				
	0,58	0,89	1,20	1,72	2,3
HR (/min)	94,70 ± 5,82	95,80 ± 3,99	93,70 ± 4,20	98,50 ± 3,40	97,50 ± 3,80
MAP (mmHg)	77,73 ± 4,58	75,93 ± 4,40	71,33 ± 3,41***	57,13 ± 2,70***	42,40 ± 2,30****
LVEDP (mmHg)	5,70 ± 0,75	6,21 ± 0,65	6,35 ± 0,65	5,60 ± 0,84	5,85 ± 0,86
CI (l/min/m²)	3,27 ± 0,32	3,13 ± 0,23	2,54 ± 0,12*	2,00 ± 0,07**	1,42 ± 0,07****
E_{es} (mmHg/mm)	137,07 ± 16,58	105,73 ± 16,72**	62,83 ± 7,83****	46,27 ± 7,26****	29,18 ± 4,15****
Pao_2 (mmHg)	171,90 ± 13,57	168,46 ± 10,52	184,36 ± 3,57	179,79 ± 5,91	178,74 ± 5,56
Sao_2 (%)	96,30 ± 1,20	97,07 ± 0,41	97,55 ± 0,20	97,53 ± 0,21	97,65 ± 0,20
$Paco_2$ (mmHg)	37,38 ± 1,94	36,64 ± 1,75	34,98 ± 1,54	34,33 ± 1,29	34,65 ± 1,31
pH	7,40 ± 0,01	7,40 ± 0,01	7,41 ± 0,01	7,42 ± 0,02	7,41 ± 0,01
Hb (g/dl)	10,66 ± 0,44	10,67 ± 0,39	10,40 ± 0,43	10,19 ± 0,34	10,07 ± 0,28
$P\bar{v}O_2$ (mmHg)	48,08 ± 2,72	48,13 ± 1,95	46,13 ± 2,49	44,25 ± 2,31	41,04 ± 1,41*
$S\bar{v}O_2$ (%)	73,74 ± 2,83	73,96 ± 2,25	69,44 ± 3,80	65,38 ± 4,45	48,21 ± 5,66**
$CaO_2 - C\bar{v}O_2$ (ml O_2/100 ml blood)	3,62 ± 0,28	3,75 ± 0,28	4,39 ± 0,43	4,87 ± 0,54*	7,71 ± 0,63****
$\dot{V}O_2$ (ml/min/m²)	113,92 ± 8,64	116,14 ± 10,10	110,74 ± 11,17	97,02 ± 10,82	101,91 ± 10,10
COD	4,35 ± 0,41	4,19 ± 0,35	3,62 ± 0,35	3,22 ± 0,32*	2,11 ± 6,17****

Statistical differences between 0,58 MAC (control values) and each subsequent concentration:
* $P < 0{,}05$.
** $P < 0{,}01$.
*** $P < 0{,}005$.
**** $P < 0{,}001$.

TABLE II. CARDIOVASCULAR EFFECTS OF INCREASING CONCENTRATIONS OF ENFLURANE (MEAN ± SE FOR 10 ANIMALS)

	Enflurane (MAC)				
	0,35	0,55	0,76	0,97	1,20
HR (/min)	96,00 ± 9,04	100,00 ± 5,92	99,00 ± 7,52	99,00 ± 7,37	102,50 ± 6,92
MAP (mmHg)	69,37 ± 4,64	70,40 ± 5,92	66,20 ± 2,47	58,40 ± 2,40	51,03 ± 2,75**
LVEDP (mmHg)	5,40 ± 0,37	6,03 ± 0,68	6,15 ± 0,54	5,44 ± 0,70	6,00 ± 0,50
CI (l/min/m²)	2,88 ± 0,27	2,47 ± 0,30	2,43 ± 0,19	2,02 ± 0,14**	1,71 ± 0,10****
E_{es} (mmHg/mm)	142,06 ± 38,55	79,31 ± 15,01	61,65 ± 9,40	41,65 ± 5,32*	28,16 ± 2,46*
Pao_2 (mmHg)	165,33 ± 13,70	188,15 ± 17,11	187,06 ± 20,43	186,46 ± 13,21*	201,39 ± 14,21*
Sao_2 (%)	97,84 ± 0,14	98,00 ± 0,17	97,80 ± 0,46	98,14 ± 0,20	98,27 ± 0,26
$Paco_2$ (mmHg)	36,82 ± 1,34	35,46 ± 1,52	36,32 ± 1,40	36,29 ± 0,67	36,20 ± 0,69
pH	7,39 ± 0,02	7,40 ± 0,01	7,40 ± 0,01	7,40 ± 0,01	7,41 ± 0,01
Hb (g/dl)	10,21 ± 0,39	10,25 ± 0,31	10,40 ± 0,35	10,26 ± 0,29	10,22 ± 0,31
$P\bar{v}o_2$ (mmHg)	43,68 ± 1,24	45,34 ± 1,74	44,62 ± 1,38	42,63 ± 1,66	39,25 ± 1,22**
$S\bar{v}o_2$ (%)	72,40 ± 1,63	73,72 ± 1,71	72,30 ± 1,72	69,55 ± 2,04	62,88 ± 1,86
$Cao_2 - C\bar{v}o_2$ (ml O_2/100 ml blood)	3,96 ± 0,24	3,88 ± 0,21	4,09 ± 0,15	4,50 ± 0,28	5,50 ± 0,28****
$\dot{V}o_2$ (ml/min/m²)	114,57 ± 14,58	95,61 ± 13,89	98,55 ± 7,73	90,79 ± 7,85*	94,11 ± 7,42*
COD	3,75 ± 0,25	3,85 ± 0,24	3,65 ± 0,18	3,34 ± 0,19	2,70 ± 0,12****

Statistical differences between 0,35 MAC (control values) and each subsequent concentration:
* $P < 0,05$.
** $P < 0,01$.
*** $P < 0,005$.
**** $P < 0,001$.

TABLE III. CARDIOVASCULAR EFFECTS OF INCREASING CONCENTRATIONS OF ISOFLURANE (MEAN ± SE FOR 10 ANIMALS)

	Isoflurane (MAC)				
	0,52	0,76	1,03	1,28	1,44
HR (/min)	114,00 ± 6,22	114,00 ± 6,34	120,00 ± 5,57	126,30 ± 4,32	125,10 ± 4,24
MAP (mmHg)	84,30 ± 6,01	79,40 ± 5,28	75,00 ± 3,65	66,07 ± 4,11**	60,73 ± 4,29**
LVEDP (mmHg)	6,01 ± 1,00	5,80 ± 1,12	6,20 ± 0,83	5,39 ± 0,96	7,02 ± 1,59
CI (l/min/m²)	2,87 ± 0,24	2,73 ± 0,22	2,68 ± 0,19	2,38 ± 0,20*	2,10 ± 0,20**
E_{es} (mmHg/mm)	225,01 ± 100,53	93,70 ± 17,22	47,69 ± 6,27*	37,40 ± 3,67*	27,88 ± 2,51*
Pao_2 (mmHg)	159,01 ± 12,57	164,94 ± 7,58	160,59 ± 8,74	162,24 ± 6,07	148,14 ± 6,28
Sao_2 (%)	96,91 ± 0,34	97,38 ± 0,28	97,25 ± 0,34	97,29 ± 0,40	97,41 ± 0,36
$Paco_2$ (mmHg)	41,10 ± 1,13	38,52 ± 1,50	39,13 ± 0,97	41,80 ± 2,74	39,69 ± 1,18
pH	7,38 ± 0,01	7,38 ± 0,28	7,38 ± 0,01	7,40 ± 0,01	7,40 ± 0,01
Hb (g/dl)	10,00 ± 0,50	10,05 ± 0,49	9,91 ± 0,46	9,59 ± 0,39	9,40 ± 0,40
$P\bar{v}o_2$ (mmHg)	45,90 ± 2,39	44,93 ± 2,16	43,95 ± 2,25	41,63 ± 1,79*	39,00 ± 1,85**
$S\bar{v}o_2$ (%)	71,84 ± 2,33	71,20 ± 2,39	70,22 ± 2,48	61,15 ± 6,53	61,18 ± 3,22**
$Cao_2 - C\bar{v}o_2$ (ml O_2/100 ml blood)	3,77 ± 0,28	3,77 ± 0,28	4,03 ± 0,29	5,00 ± 0,81	5,15 ± 0,57*
$\dot{V}o_2$ (ml/min/m²)	103,95 ± 5,79	103,95 ± 5,79	103,77 ± 5,44	117,49 ± 22,80	98,49 ± 3,80
COD	3,86 ± 0,29	3,86 ± 0,29	3,60 ± 0,28	3,10 ± 0,32*	2,76 ± 0,22****

Statistical differences between 0,52 MAC (control values) and each subsequent concentration:
* $P < 0,05$.
** $P < 0,01$.
*** $P < 0,005$.
**** $P < 0,001$.

decreased significantly once enflurane 0,97 and 1,20 MAC was administered and the result of the CI and $\dot{V}o_2$ interaction resulted in a decrease in COD and an increase in $(a - \bar{v})\ Do_2$ at 1,20 MAC enflurane.

Isoflurane (Table III)

The CI was significantly decreased at 1,28 and 1,44 MAC isoflurane. Again the decrease in myocardial contractility (E_{es}) was responsible for the reduction in flow. $\dot{V}o_2$ remained constant, and owing to the reduction in CI and the stable $\dot{V}o_2$, the $(a - \bar{v})\ Do_2$ was increased when 1,28 and 1,44 MAC isoflurane was administered. This reduction in the O_2 supply/demand ratio is also reflected in the COD.

Discussion

An effective CI is defined as the blood flow that will meet oxygen demands.[9] Apart from providing analgesia and hypnosis, one of the aims of anaesthesia is to maintain aerobic

cellular oxygenation, and hence the maintenance of an effective CO is of paramount importance. However, during anaesthesia the $\dot{V}O_2$ usually decreases[10,11] and intuitively it is expected that the depression of myocardial contractility associated with the commonly used inhalational anaesthetic agents,[12] may be of little consequence to the normal patient. Furthermore, if the modifying factors of the circulation, i.e. the HR, preload and afterload, changes in a favourable direction, it may well overcome the depression of myocardial contractility caused by halothane, enflurane and isoflurane.

The problem is to evaluate the effectiveness of the circulation in terms of the definition put forward by Braunwald.[9] For this particular study we chose to use $S\bar{v}O_2$, $P\bar{v}O_2$ and COD as indices of change in cellular oxygenation. The rationale for these parameters can be found in the Fick equation:

$$\dot{V}O_2 = CO(CaO_2 - C\bar{v}O_2) \quad \ldots\ldots (1).$$

Theoretical analysis by Tenney[13] and a study by Krasnitz *et al.*[14] indicate that cellular oxygen tension relates to venous oxygen tension. Because of the relative linear shape of the oxyhaemoglobin dissociation curve at the venous PO_2 range, it can, for practical purposes, be accepted that $P\bar{v}O_2$ relates directly to $S\bar{v}O_2$. The latter is an important component in the calculation of CaO_2. To prove the point, Krasnitz *et al.*[14] demonstrated that in patients with acute circulatory disorders, a reduction in $S\bar{v}O_2$ below 60% was associated with an exponential increase in blood lactate concentrations and an increased mortality.

The various factors which affect cellular oxygenation can then be evaluated with reference to a rearranged Fick equation:

$$C\bar{v}O_2 = CaO_2 - \dot{V}O_2/CO \quad \ldots\ldots (2)$$

$$\text{Cellular } PO_2 \simeq CaO_2 - \dot{V}O_2/CO \quad \ldots\ldots (3)$$

Provided the PaO_2 remains above 8 kPa, it should not affect the $S\bar{v}O_2$.[15] In our experimental study the SaO_2 remained above 90% (Tables I - III) and hence CaO_2 did not change significantly. Cellular oxygenation is therefore determined by the ratio of $\dot{V}O_2/CO$ (equation 2).

However, in order to incorporate variation in CaO_2, the relationship of $\dot{V}O_2$ to oxygen supply (DO_2) can be used:

$$COD = DO_2/\dot{V}O_2 \quad \ldots\ldots (4)$$

$$= CO.CaO_2/[CO(CaO_2 - C\bar{v}O_2)] \quad \ldots\ldots (5)$$

$$= CaO_2/(CaO_2 - C\bar{v}O_2),$$

where COD = coefficient of oxygen delivery[7] with the normal value = 4.

Before evaluating the data from this study, one should be reminded of the two basic mechanisms available to the body by which aerobic $\dot{V}O_2$ can be maintained. Equation 1 predicts that an increase in $\dot{V}O_2$ could be accommodated either by an increase in CO (and an increase in capillary density) — the so-called vascular reserve — or by means of an increase in $(a - \bar{v})\,DO_2$, the 'metabolic' reserve.[16] The CO is the primary buffer under non-exercise conditions and once $(a - \bar{v})DO_2$ decreases, it signifies that the circulation is at some critical value and hence the secondary mechanism must be employed.

Results from this study indicate that the COD and $(a - \bar{v})\,DO_2$ started to change at approximately similar MAC values (Figs 2 and 3). Although statistical analysis was not applied to verify this, Figs 1 and 2 demonstrate tendencies that support this concept. Because equipotent concentrations of the inhalational agents were not used, statistical comparisons between the gases were not attempted.

The CO is a function of HR and SV. SV is again determined by preload, afterload and contractility. Detailed analysis of the effect of the three drugs on myocardial contractility has been published elsewhere.[12] We have demonstrated that halothane caused the least myocardial depression and there is little difference between enflurane and isoflurane, although both were associated with more myocardial depression than halothane. Given this fact, why would the circulation become 'critical' at similar MAC values? To answer the question one must look at the modifying factors of the circulation, i.e. HR and pre- and afterload.

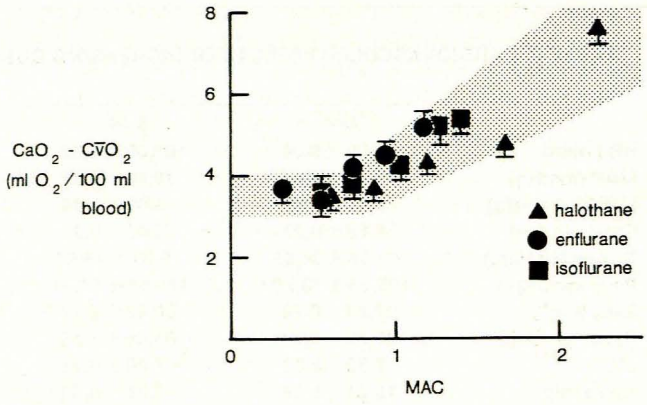

Fig. 2. The arterial-venous oxygen difference $[(a - \bar{v})DO_2]$ plotted against MAC multiples for halothane, enflurane and isoflurane. The $(a - \bar{v})DO_2$ demonstrates an increasing tendency from approximately 1 MAC.

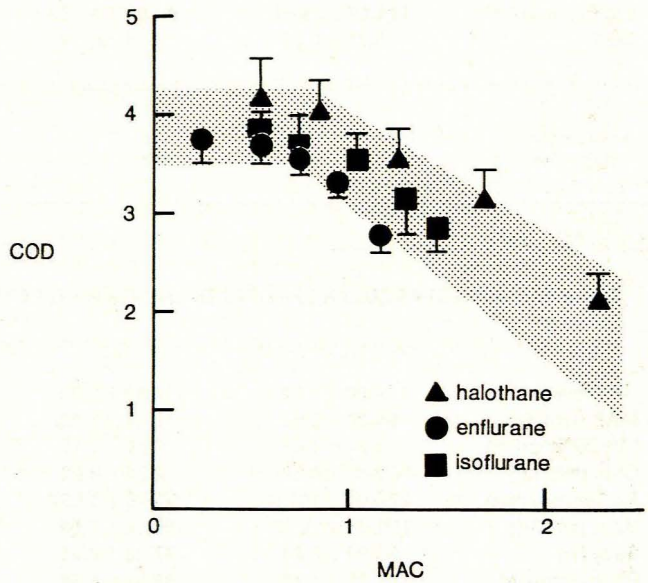

Fig. 3. The coefficient of oxygen delivery (COD) starts to decrease at approximately 1 MAC. The turning point for the COD coincides with the MAC value at which the $(a - \bar{v})\,DO_2$ started to increase.

Clearly the isoflurane produced a higher mean HR than enflurane or halothane. This could to some extent compensate for the myocardial depression that followed isoflurane administration. Although halothane caused less myocardial depression, it was penalised by a slower HR and higher blood pressure (index of afterload), while enflurane had the advantage of a lower afterload that could overcome the myocardial depression caused by increasing concentrations of the drug.

The limitations of the results from the open-chested animal model applied to human physiology must be kept in mind. The MAC value at which the circulation became critical appears to be low if one considers that higher concentration than this is often encountered in clinical practice. A possible explanation for this is the fact that no surgery was done during actual experimentation and the lack of a surgical stimulus coupled with the tight control of the $PaCO_2$ were most probably responsible for lower cardiac indices in our experimental animals compared with clinical practice (especially in spontaneously breathing patients). However, we do believe that our results, obtained under carefully controlled conditions, give

valuable insight into oxygen delivery during inhalational anaesthesia.

If the effect on the circulation appears to be of equal magnitude (with reference to cellular oxygenation), the indications for use in everyday clinical practice can be discussed. In the patient with normal myocardial reserve, it is probably immaterial which drug is used. The deciding factor will in these cases probably relate to cost and availability. In the patient with poor systolic reserve of the myocardium, i.e. either overt failure or a history of myocardial failure, the drug with the least myocardial depression, i.e. halothane, is preferable. However, the maintenance of the MAP with halothane may be detrimental to the SV, and the use of other anaesthetic drugs that cause a slight reduction in MAP will be of obvious benefit. Drugs like opiates and droperidol will be useful (in small doses) and the direct vasodilators will also assist the ejection of the SV in the heart with depressed function.

The patient with ischaemic heart disease requires a slower HR and maintenance of diastolic arterial pressure. Halothane seems to be the agent of choice, while enflurane, with its associated decrease in MAP, should not be the primary choice. Isoflurane, apart from the fact that it can induce coronary 'steal',[17] is also responsible for a tachycardia. The latter, in the non-failing heart, will limit oxygen supply to the myocardium due to the decrease in diastolic time.[18] In the failing heart, which dilates if subjected to an increase in HR, it will cause an increase in myocardial tension and therefore oxygen consumption and, coupled with the limited diastolic period for perfusion to the LV, can precipitate cellular hypoxia.

Clinical evaluation of the patient with reference to congestive symptoms, exercise tolerance or, if available, more invasive measurements, coupled with the basic physiology of the circulation as discussed, may serve to ensure the rational use of the three available potent inhalational anaesthetic vapours.

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