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Tolerance to Acute Isovolemic Hemodilution

Effect of Anesthetic Depth

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Background: **Acceptance of a lower transfusion trigger in the perioperative period requires study of the effects of anesthetic depth on the tolerance to acute isovolemic anemia. Anesthetic agents with negative effects on the cardiovascular system may exert proportionately greater depressant effects on cardiac output response than on tissue oxygen demand, reducing tolerance to acute isovolemic anemia.**

Methods: **In the first study, animals were anesthetized with halothane (n = 14; 23.8 ± 4.8 kg, mean ± SD). In a second study, animals were anesthetized with ketamine (n = 14; 24.3 ± 4.7 kg). In each study, dogs were randomly allocated to receive either low or high concentrations of anesthetic. Oxygen delivery and oxygen consumption were determined from independent measurements during a stepwise isovolemic hemodilution protocol. In each dog, critical oxygen delivery was determined from a plot of oxygen consumption *versus* oxygen delivery using a least-sum-of-squares technique. Critical hemoglobin (hemoglobin) was determined from a plot of hemoglobin *versus* oxygen consumption using the same method.**

Results: **With both agents, the higher anesthetic concentration was associated with decreased oxygen consumption, resulting in a lower critical oxygen delivery. However, critical hemoglobin was significantly higher in the animals receiving the higher anesthetic dosage (1.5 *vs.* 1.0 minimum alveolar concentration of halothane: 4.1 ± 1.3 *vs.* 2.3 ± 0.5 g/dl, $P < 0.05$; high- *vs.* low-dose ketamine: 3.7 ± 1.4 *vs.* 2.5 ± 0.6 g/dl, $P < 0.05$). This was related to a marked blunting of the cardiac output response to hemodilution in the animals receiving the higher anesthetic dosage.**

Conclusions: **Increased anesthetic depth with halothane or ketamine resulted in a decreased tolerance to acute anemia, as reflected by a significant increase in critical hemoglobin concentration.**

ADEQUATE tissue oxygenation during acute normovolemic anemia is maintained by both an increase in cardiac output (CO) and an increase in tissue oxygen extraction.[1,2] The increase in CO is related to the reduction in blood viscosity resulting in increased venous return and decreased ventricular afterload[3,4] as well as an increased sympathetic stimulation of the heart.[5,6] Tissue oxygen extraction is increased at the systemic level by the redistribution of blood flow according to regional metabolic demand[7] and at the microcirculatory level by a better spatial and temporal distribution of the red blood cells into the capillary network.[8] When these compensatory mechanisms are exhausted, oxygen uptake starts to fall and becomes delivery dependent.[9,10] Under these conditions, tissue hypoxia develops as reflected by an abrupt rise in blood lactate concentrations.[10,11] The hemoglobin concentration (hemoglobin) at which this phenomenon occurs is defined as the critical hemoglobin.[9,10,12]

Recent acceptance of a lower transfusion trigger in the perioperative period has raised the question of the effects of anesthetic depth on the tolerance to acute isovolemic anemia. Anesthetic agents are known to decrease systemic oxygen uptake[13,14] in a dose-dependent way. This implies that a higher anesthetic level could be associated with a lower critical oxygen delivery (*i.e.*, the value of oxygen delivery below which oxygen consumption becomes supply dependent). These apparent beneficial effects of a higher anesthetic depth on the tissue oxygen balance might be counterbalanced by the effects of anesthetic agents on the cardiovascular system. Indeed, anesthetic agents could alter the compensatory mechanisms implicated during isovolemic hemodilution, especially the CO response. This effect may be directly related to the vasodilating and negative inotropic effects of the anesthetic agents and/or indirectly related to the blunting of the sympathetic system activity.[15,16]

We hypothesized that the negative cardiovascular effects of anesthetic agents may exceed their effects on tissue metabolism, so that increasing the level of anesthesia may reduce tolerance to acute isovolemic anemia and increase the critical hemoglobin. We tested this hypothesis in a dog model of stepwise isovolemic hemodilution. In the first study, we assessed the effects of halothane, a volatile anesthetic with well-known cardiovascular depressant properties.[17,18] In a subsequent study, we evaluated the effects of ketamine, an agent with unique cardiovascular stimulant properties[19] related primarily to direct stimulation of central nervous system structures.[20,21]

Materials and Methods

Procedures

All experimental procedures were performed in accordance with the Belgian guidelines for care of laboratory animals and were approved by the animal research committee of the School of Medicine of the Free University of Brussels (Brussels, Belgium). Twenty-eight mongrel

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dogs were studied. In the first study, animals were anesthetized with halothane (n = 14; weight 23.8 ± 4.8 kg). After administration of intravenous thiopental 20 mg/kg, tracheal intubation was performed, and mechanical ventilation was started (Elema 900B; Siemens, Solna, Sweden) with air. Ventilatory frequency was set at 12 min^{-1}, and tidal volume was adapted to maintain an arterial partial pressure of carbon dioxide ($Paco_2$) of approximately 35 mmHg. Respiratory conditions remained unchanged until the end of the study. Anesthesia was maintained with halothane, anesthetic depth being adapted to the surgical stimulation of the experimental protocol (end-tidal minimum alveolar concentration [MAC] between 1.0 and 2.0). After completion of the surgical procedure, the dogs were randomly allocated to receive either 1.0 MAC halothane (0.96%; n = 7) or 1.5 MAC halothane (1.4%; n = 7).[22]

In a subsequent study, animals were anesthetized with ketamine (n = 14; 24.3 ± 4.7 kg). In this group, dogs were randomly allocated to receive ketamine either at low dose (an induction bolus of 5 mg/kg followed by a continuous infusion of 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$; n = 7) or at high dose (an induction bolus of 10 mg/kg followed by a continuous infusion of 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$; n = 7). After tracheal intubation was performed, controlled mechanical ventilation was started with respiratory conditions as described previously.

In both studies, animals received pancuronium bromide to facilitate controlled ventilation. This agent was given as an initial bolus of 0.1 mg/kg followed by hourly boluses of 1–2 mg.

Electrodes were attached to the four limbs for monitoring heart rate (HR). Two catheters (16-gauge; Becton Dickinson and Co., Rutherford, NJ) were inserted: one into a peripheral vein for fluids and drug infusion and one into the distal aorta through a femoral artery for monitoring of blood pressure and sampling of arterial blood. A pulmonary arterial catheter (Swan-Ganz catheter, model 93A-131-7F; Baxter Healthcare, Irvine, CA) was inserted through a jugular vein. A gas analyzer (Capnomac AGM 103; Datex, Helsinki, Finland) was inserted in the respiratory breathing system for monitoring of end-tidal carbon dioxide tension ($Petco_2$) and halothane concentration. Exhaled gases were directed through a mixing chamber for sampling to measure mixed expired oxygen fraction (Feo_2) using a paramagnetic method (semirapid oxygen analyzer, model 500D PK; Morgan Co., Chatam, United Kingdom). The oxygen analyzer and the capnometer were calibrated before each experiment. Expired minute ventilation was measured with a spirometer (model Magtrak II, London, United Kingdom) located proximal to the mixing chamber. Respiratory circuit was carefully checked for air leakage before each experiment.

A splenectomy was performed through a midline laparotomy to prevent autotransfusion. To compensate for insensible fluid losses, the dogs received an intravenous infusion of 0.9% sodium chloride at a rate of 10 ml/kg during the splenectomy and 1 $ml \cdot kg^{-1} \cdot h^{-1}$ thereafter, until the end of the experiment. Body temperature was maintained at 36–38°C throughout the study using warming blankets and humidified heated gases.

Heart rate, arterial pressure, and pulmonary arterial pressure were monitored continuously (Sirecust; Siemens AG, Erlangen, Germany) and recorded together with $Petco_2$ and Feo_2 (model 8000S; Gould Electronique, Ballainvilliers, France). Zero pressure was set at the midchest level of the animal.

Heart rate and intravascular pressures, including mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary arterial occlusion pressure, and right atrial pressure, were measured at end-expiration from the paper trace. Feo_2 and $Petco_2$ were measured from the paper trace over 1 min. Expired volume was measured over the same period. CO was measured with the thermodilution technique (module E 2261/A; Siemens AG) by repeated injections of 10 ml cold (<5°C) dextrose, 5%, in water. Each injection was started at the end of expiration.[23] Three to five measurements, with a variability of less than 10%, were averaged for each CO measurement. Immediately thereafter, arterial and mixed venous blood samples were withdrawn for measurement of blood gas tensions (ABL 2; Radiometer, Copenhagen, Denmark). Hemoglobin and oxygen saturation were measured using a CO oximeter calibrated for dog's blood (OSM 3; Radiometer). Each sample was analyzed twice, and the two values were averaged. Arterial blood lactate concentration (lactate) was measured enzymatically using an automated analyzer (Kontron, Basel, Switzerland).

Cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR), left ventricular stroke work index, and arterial and mixed venous oxygen content were calculated using standard formulae. Oxygen delivery (Do_2) was calculated from CO measurements and arterial oxygen content and indexed for weight. Oxygen consumption ($\dot{V}o_2$) was calculated from measured Feo_2 and minute ventilation, using the appropriate mass balance equation and accounting for the difference between inspired and expired nitrogen fraction, indexed for weight.[24] Oxygen extraction (O_2ER) was obtained by dividing $\dot{V}o_2$ by Do_2.

Baseline measurements were performed 30 min after completion of splenectomy. Each animal was then slowly hemodiluted by repeated withdrawals of 5-ml/kg aliquots of arterial blood simultaneously replaced by the same volume of 6% hydroxyethyl starch, 200/0.5 (Haes Steril 6%; Fresenius AG, Bad Hombourg, Germany). After each exchange procedure, a 10-min period was allowed to achieve a new steady state defined by a stable MAP, $Petco_2$, and Feo_2. The exchange procedure was continued until the animal could no longer maintain a stable

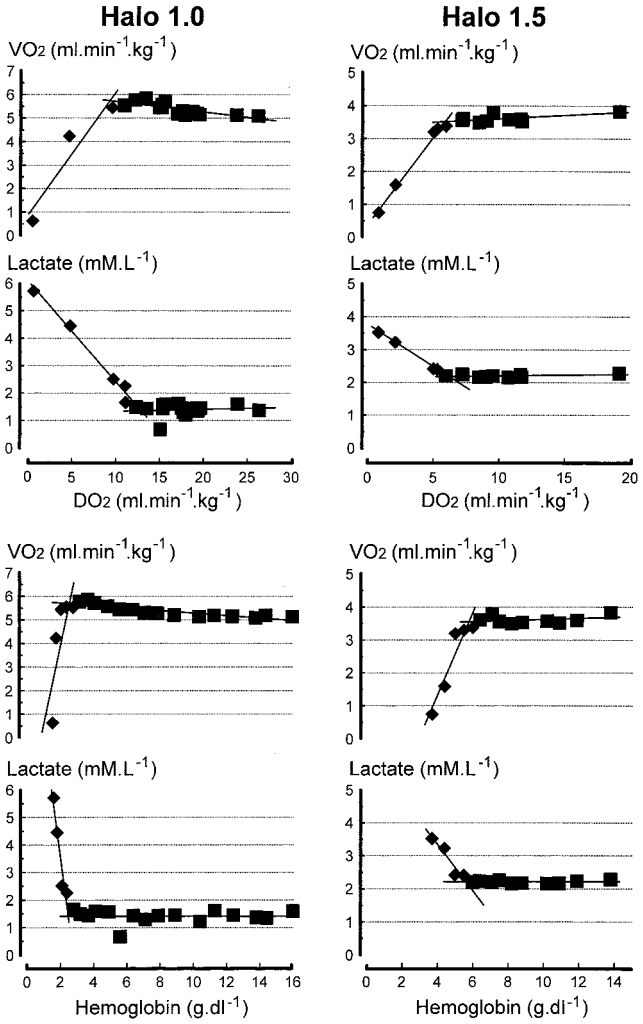

Fig. 1. Representative examples of the (*top*) oxygen consumption ($\dot{V}o_2$)–oxygen delivery (Do_2), lactate–Do_2 and (*bottom*) $\dot{V}o_2$–hemoglobin, and lactate–hemoglobin relationships in the 1.0 MAC halothane (Halo 1.0, *left*) and 1.5 MAC halothane (Halo 1.5, *right*) groups.

arterial pressure. Death followed shortly thereafter, with the animal still anesthetized.

Statistical Analysis

In each animal, critical Do_2 was determined from a plot of $\dot{V}o_2$ *versus* Do_2 using the dual lines regression method.[25] Critical Do_2 was defined as the point of intersection of the two best-fit regression lines as determined by a least sum of squares technique. Critical O_2ER was calculated as the ratio of $\dot{V}o_2/Do_2$ at critical point. Critical Do_2 was also determined in each animal using the same dual regression lines analysis from a plot of lactate *versus* Do_2. The critical value of hemoglobin was determined using the same mathematical analysis from a plot of $\dot{V}o_2$ *versus* hemoglobin (hemoglobin from $\dot{V}o_2$) and from a plot of lactate *versus* hemoglobin (hemoglobin from lactate). Figures 1 and 2 illustrate the $\dot{V}o_2$–Do_2, lactate–Do_2, $\dot{V}o_2$–hemoglobin, and lactate–hemoglobin relationships that were obtained in each dog in the halothane and ketamine studies.

The hemoglobin–Do_2 relationship was also analyzed in each animal by determining the polynomial that best fit the data. Equations of these polynomials were used to determine Do_2 values corresponding to fixed hemoglobin values. This allowed for comparison of the Do_2 response to progressive hemodilution between the two anesthetic dosages in the halothane and the ketamine study.

For both halothane and ketamine, sample size was calculated to detect a difference in critical hemoglobin of 40% between the two anesthetic dosages with a power of 0.8 and an α of 0.05.

Hemodynamic and respiratory variables obtained at baseline and at the experimental point closest to critical Do_2 with the two anesthetic dosages were compared using a two-way analysis of variance, followed by pair-

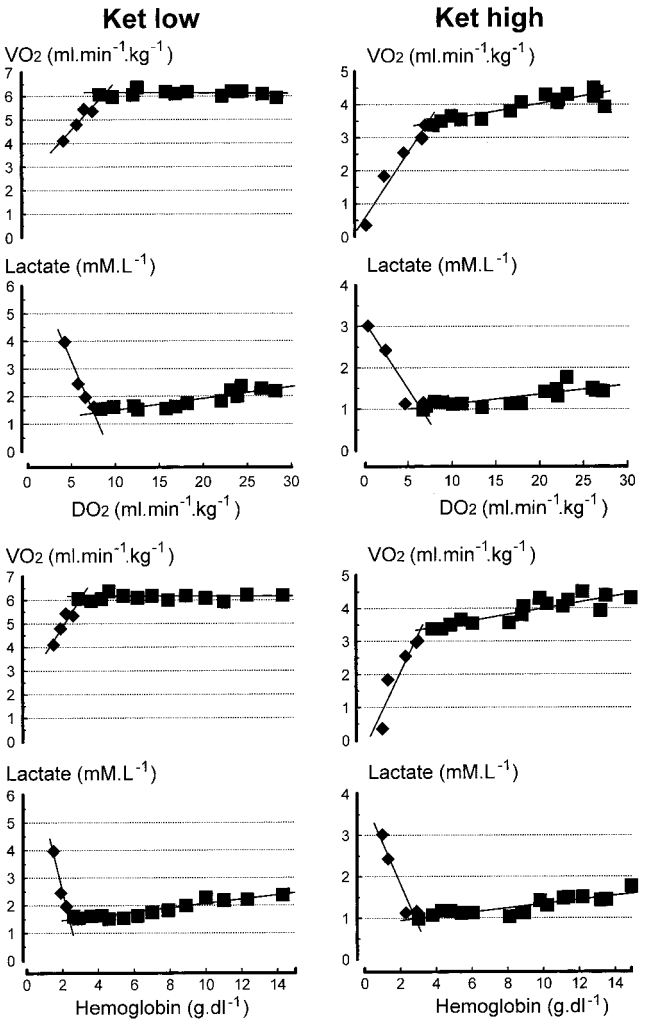

Fig. 2. Representative examples of the (*top*) oxygen consumption ($\dot{V}o_2$)–oxygen delivery (Do_2), lactate–Do_2 and (*bottom*) $\dot{V}o_2$–hemoglobin, and lactate–hemoglobin relationships in the low-dose ketamine (Ket low, *left*) and high-dose ketamine (Ket high, *right*) groups.

Table 1. Hemodynamic and O_2-derived Variables in the Halothane Groups

Variables/Groups	Baseline	Just before Critical Point
Body temp (°C)		
Halo 1.0	37.5 ± 1.3	36.6 ± 1.7
Halo 1.5	37.0 ± 0.8	35.9 ± 0.8
Heart rate (min^{-1})		
Halo 1.0	147 ± 27	161 ± 38
Halo 1.5	119 ± 9	116 ± 15*
MAP (mmHg)		
Halo 1.0	100 ± 20	67 ± 16##
Halo 1.5	66 ± 12**	43 ± 7*#
MPAP (mmHg)		
Halo 1.0	11.7 ± 2.3	15.6 ± 4.8
Halo 1.5	12.2 ± 3.1	13.4 ± 4.3
PAOP (mmHg)		
Halo 1.0	4.1 ± 1.6	3.7 ± 1.5
Halo 1.5	7.0 ± 3.3	8.7 ± 3.6*
RAP (mmHg)		
Halo 1.0	2.9 ± 1.5	3.5 ± 1.9
Halo 1.5	4.6 ± 1.9	5.4 ± 2.1
CI ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Halo 1.0	124 ± 33	235 ± 88##
Halo 1.5	93 ± 19*	107 ± 47**
SI ($ml \cdot kg^{-1}$)		
Halo 1.0	0.85 ± 0.17	1.43 ± 0.30##
Halo 1.5	0.78 ± 0.17	0.91 ± 0.29**
SVR ($d \cdot s \cdot cm^{-5}$)		
Halo 1.0	2937 ± 694	1102 ± 427##
Halo 1.5	2187 ± 533	1317 ± 587##
LVSWI ($g \cdot m \cdot kg^{-1}$)		
Halo 1.0	1.09 ± 0.21	1.23 ± 0.44
Halo 1.5	0.62 ± 0.16*	0.42 ± 0.16**
Hb ($g \cdot dl^{-1}$)		
Halo 1.0	13.1 ± 3.0	2.9 ± 0.6##
Halo 1.5	12.5 ± 1.1	4.5 ± 1.6##
pHa (U)		
Halo 1.0	7.38 ± 0.05	7.27 ± 0.09##
Halo 1.5	7.35 ± 0.03	7.31 ± 0.05
$Paco_2$ (mmHg)		
Halo 1.0	31.7 ± 3.4	35.5 ± 5.3
Halo 1.5	33.2 ± 2.4	32.7 ± 3.9
Sao_2 (%)		
Halo 1.0	94 ± 1	92 ± 7.0
Halo 1.5	94 ± 1	95 ± 1.5
Svo_2 (%)		
Halo 1.0	76 ± 5	46 ± 11##
Halo 1.5	71 ± 7	47 ± 10##
Cao_2 ($ml \cdot dl^{-1}$)		
Halo 1.0	17.4 ± 3.8	4.0 ± 1.0##
Halo 1.5	16.6 ± 2.6	6.2 ± 2.2##
Cvo_2 ($ml \cdot dl^{-1}$)		
Halo 1.0	14.0 ± 3.3	2.0 ± 0.8##
Halo 1.5	12.5 ± 2.9	3.1 ± 1.5##
Do_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Halo 1.0	21.1 ± 5.3	8.7 ± 1.8##
Halo 1.5	15.4 ± 3.9*	5.9 ± 0.9##
Vo_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Halo 1.0	4.1 ± 1.0	4.5 ± 1.1
Halo 1.5	3.5 ± 0.2	3.0 ± 0.4
O_2ER (%)		
Halo 1.0	19.8 ± 4.2	52.4 ± 14.0##
Halo 1.5	24.5 ± 7.5	60 ± 6.0##
Lactate (mM^{-1})		
Halo 1.0	2.3 ± 1.2	2.7 ± 1.5
Halo 1.5	2.8 ± 1.1	2.9 ± 1.1

Data are expressed as mean ± SD.

* $P < 0.05$, ** $P < 0.01$ *vs.* Halo 1.0; # $P < 0.005$, ## $P < 0.01$ *vs.* baseline.

Body temp = central body temperature; Cao_2 = arterial oxygen content; CI = cardiac index; Cvo_2 = mixed venous oxygen content; Do_2 = oxygen delivery indexed for weight; Halo 1.0 = halothane 1.0 MAC; Halo 1.5 = halothane 1.5 MAC; Hb = hemoglobin concentration; lactate = arterial blood lactate concentration; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; O_2ER = oxygen extraction ratio; $Paco_2$ = arterial partial pressure of carbon dioxide; PAOP = pulmonary arterial occlusion pressure; pHa = arterial pH; RAP = right atrial pressure; Sao_2 = arterial oxygen saturation; SI = stroke index; Svo_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance; Vo_2 = oxygen consumption indexed for weight.

wise comparisons using a Tukey honest significance difference *post hoc* test. Data obtained at critical point in the two anesthetic levels were compared using the Mann–Whitney U test. In each group, the hemoglobin–Do_2 relationship was compared between the two anesthetic dosages using a two-way analysis of variance for repeated measurements. Because anesthetic depth between both agents could not be compared, no statistical analysis was performed between data obtained with the two anesthetic agents.

All values are expressed as mean ± SD. A *P* value less than 0.05 was considered statistically significant.

Results

Halothane Anesthesia

Hemodynamic and Oxygen-derived Variables. In all animals, acute isovolemic hemodilution resulted in a significant decrease in MAP and in SVR (table 1). In the 1.0 MAC halothane group, CI increased, mainly through an increase in SI. In the 1.5 MAC halothane group, neither CI nor SI increased. As compared to 1.0 MAC, 1.5 MAC halothane anesthesia resulted in a lower HR and MAP, a higher pulmonary arterial occlusion pressure, and a lower CI, SI, and left ventricular stroke work index. Between the two anesthetic dosages, there was a significantly different response to acute hemodilution for CI and SI. In all dogs, acute isovolemic hemodilution resulted in a decrease in mixed venous oxygen saturation. Do_2 decreased but $\dot{V}o_2$ remained constant as O_2ER increased (table 1). Just before the critical point, hemoglobin tended to be higher, and $\dot{V}o_2$ to be lower, in the 1.5 MAC halothane group.

Data at Critical Point. Critical Do_2 was significantly lower in the 1.5 MAC halothane group (table 2). This was due to a lower critical $\dot{V}o_2$ as critical O_2ER was not significantly different between the two groups. Critical Do_2 obtained from lactate was also significantly lower in

Table 2. Data at Critical Point in the Halothane Groups

	Halo 1.0	Halo 1.5
Do_2 (ml · min^{-1} · kg^{-1})	8.2 ± 2.0	5.4 ± 1.0*
Vo_2 (ml · min^{-1} · kg^{-1})	4.5 ± 1.1	3.6 ± 0.3*
O_2Er (%)	57.4 ± 14.9	66.8 ± 9.4
Do_2 from lactate (ml · min^{-1} · kg^{-1})	8.5 ± 2.7	5.9 ± 1.3*
Lactate (mM^{-1})	2.4 ± 1.1	2.9 ± 1.3
Hb from Vo_2 (g · dl^{-1})	2.3 ± 0.5	4.1 ± 1.3*
Hb from lactate (g · dl^{-1})	2.6 ± 0.9	4.4 ± 1.6

Data are expressed as mean ± SD.

* $P < 0.05$ *vs.* Halo 1.0.

Do_2 = oxygen delivery indexed for weight; Do_2 from lactate = oxygen delivery indexed for weight obtained from lactate measurements; Halo 1.0 = halothane 1 MAC; Halo 1.5 = halothane 1.5 MAC; Hb from lactate = hemoglobin concentration obtained from lactate measurements; Hb from Vo_2 = hemoglobin concentration obtained from Vo_2 measurements; O_2ER = oxygen extraction ratio; Vo_2 = oxygen consumption indexed for weight.

the 1.5 MAC halothane group. Lactate at the critical point was not different in the 1.5 MAC halothane and 1.0 MAC halothane groups. Critical hemoglobin obtained through either $\dot{V}o_2$ or lactate was significantly higher in the 1.5 MAC halothane group than in the 1.0 MAC halothane group. $\dot{V}o_2$ at critical hemoglobin was lower in the 1.5 MAC halothane group than in the 1.0 MAC halothane group (3.6 ± 0.3 and 4.5 ± 1.2 ml · min^{-1} · kg^{-1}, respectively; $P < 0.05$). Lactate at critical hemoglobin was not different between the two groups (1.5 MAC halothane: 2.8 ± 1.1 mM/l; 1.0 MAC halothane: 2.0 ± 1.0 mM/l.

Hemoglobin–Do_2 Relationship. With the two anesthetic concentrations, isovolemic hemodilution resulted in a progressive decrease in Do_2 (fig. 3, *top*). Do_2 changes in response to the stepwise decrease in hemoglobin concentration were significantly different among the two halothane concentrations.

Ketamine Anesthesia

Hemodynamic and Oxygen-derived Variables. In all animals, acute isovolemic hemodilution resulted in a significant decrease in MAP (table 3). In the low-dose ketamine group, CI increased, mainly through an increase in SI. SVR decreased. In the high-dose ketamine group, neither CI nor SI increased. As compared to low-dose ketamine, high-dose ketamine resulted in a lower HR and MPAP, a higher SVR, and a lower CI, SI, and left ventricular stroke work index (table 3). Between the two anesthetic dosages, there was a significantly different response to acute hemodilution for HR, CI, SI, and SVR. In all dogs, acute isovolemic hemodilution resulted in a decrease in arterial pH and mixed venous oxygen saturation. Do_2 decreased but $\dot{V}o_2$ remained constant as O_2ER increased (table 3). Just before the critical point, hemoglobin concentration tended to be higher and $\dot{V}o_2$ was significantly lower in the high-dose ketamine group.

Data at Critical Point. Critical Do_2 was significantly lower in the high-dose ketamine group (table 4). This was due to a lower critical $\dot{V}o_2$ as critical O_2ER was not significantly different between the two groups. Critical Do_2 obtained from lactate was also significantly lower in the high-dose ketamine group. Critical hemoglobin obtained from $\dot{V}o_2$ was significantly higher in the high-dose ketamine group. $\dot{V}o_2$ at critical hemoglobin was significantly lower in the high-dose ketamine group than in the low-dose ketamine group (4.4 ± 1.2 and 6.0 ± 0.9 ml · min^{-1} · kg^{-1}, respectively; $P < 0.05$). Critical hemoglobin obtained from lactate tended to be higher in the high-dose ketamine group, although the difference did not reach statistical significance. Lactate at critical hemoglobin was not different between the two groups (high-dose ketamine: 1.7 ± 0.7 mM/l; low-dose ketamine: 1.8 ± 0.8 mM/l.

Hemoglobin–Do_2 Relationship. With the two anesthetic concentrations, isovolemic hemodilution resulted in a progressive decrease in Do_2 (fig. 3, *bottom*). Do_2 changes in response to the stepwise decrease in hemoglobin concentration were significantly different among the two ketamine dosages.

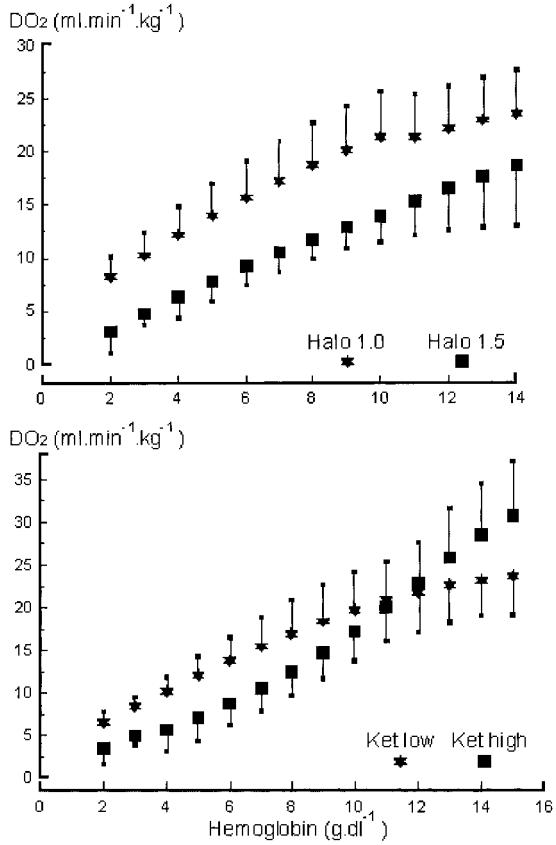

Fig. 3. (*Top*) Hemoglobin–oxygen delivery (Do_2) relationship in the two halothane groups during stepwise hemodilution. *Stars* = halothane 1.0 MAC group; *squares* = halothane 1.5 MAC group. (*Bottom*) Hemoglobin–Do_2 relationship in the two ketamine groups during stepwise hemodilution. *Stars* = ketamine low-dose group; *squares* = ketamine high-dose group.

Table 3. Hemodynamic and O_2-derived Variables in the Ketamine Groups

Variables/Groups	Baseline	Just before Critical Point
Body temp (°C)		
Ket low	38.3 ± 0.5	38.0 ± 0.3
Ket high	38.2 ± 0.5	37.2 ± 1.1
Heart rate (min^{-1})		
Ket low	174 ± 24	191 ± 28
Ket high	170 ± 28	144 ± 23*
MAP (mmHg)		
Ket low	141 ± 18	85 ± 13##
Ket high	115 ± 25	81 ± 15##
MPAP (mmHg)		
Ket low	17.8 ± 3.9	20.6 ± 4.4
Ket high	14.6 ± 2.1	13.2 ± 2.6**
PAOP (mmHg)		
Ket low	5.4 ± 2.5	4.6 ± 1.4
Ket high	3.6 ± 1.0	4.9 ± 2.2
RAP (mmHg)		
Ket low	5.1 ± 2.1	3.6 ± 1.4
Ket high	1.9 ± 0.7**	2.6 ± 1.7
CI ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Ket low	132 ± 26	252 ± 55##
Ket high	139 ± 28	121 ± 35**
SI ($ml \cdot kg^{-1}$)		
Ket low	0.77 ± 0.16	1.33 ± 0.25##
Ket high	0.83 ± 0.16	0.84 ± 0.21**
SVR ($d \cdot s \cdot cm^{-5}$)		
Ket low	3127 ± 860	1055 ± 537##
Ket high	3115 ± 970	2698 ± 1484*
LVSWI ($g \cdot m \cdot kg^{-1}$)		
Ket low	1.42 ± 0.41	1.44 ± 0.29
Ket high	1.25 ± 0.39	0.88 ± 0.29*
Hb ($g \cdot dl^{-1}$)		
Ket low	13.9 ± 1.0	2.8 ± 0.7##
Ket high	14.4 ± 2.3	4.7 ± 2.0##
pHa (U)		
Ket low	7.37 ± 0.05	7.24 ± 0.08##
Ket high	7.36 ± 0.03	7.27 ± 0.06#
$Paco_2$ (mmHg)		
Ket low	35.4 ± 4.3	39.4 ± 6.4
Ket high	32.4 ± 2.7	33.9 ± 4.2
Sao_2 (%)		
Ket low	92 ± 3	91 ± 5
Ket high	95 ± 2	96 ± 2*
Svo_2 (%)		
Ket low	73 ± 8	37 ± 9##
Ket high	78 ± 3	44 ± 7##
Cao_2 ($ml \cdot dl^{-1}$)		
Ket low	18.1 ± 1.5	3.7 ± 0.9##
Ket high	19.3 ± 3.0	6.6 ± 2.6##
Cvo_2 ($ml \cdot dl^{-1}$)		
Ket low	14.3 ± 1.7	1.5 ± 0.6##
Ket high	15.8 ± 2.7	3.0 ± 1.4##
Do_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Ket low	23.8 ± 4.3	9.0 ± 1.2##
Ket high	27.9 ± 6.7	7.5 ± 1.6##
Vo_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)		
Ket low	5.8 ± 0.8	5.8 ± 0.8
Ket high	4.8 ± 0.8	4.2 ± 0.8**
O_2ER (%)		
Ket low	25.6 ± 8.4	64.6 ± 6.8##
Ket high	17.6 ± 3.1	56.2 ± 7.1##
Lactate (mM^{-1})		
Ket low	2.0 ± 0.6	2.2 ± 1.0
Ket high	1.9 ± 0.7	1.7 ± 0.7

(continues)

Table 3. (continued)

Data are expressed as mean ± SD.

* $P < 0.05$, ** $P < 0.01$ *vs.* Ket low; # $P < 0.05$, ## P *vs.* baseline.

Body temp = central body temperature; Cao_2 = arterial oxygen content; CI = cardiac index; Cvo_2 = mixed venous oxygen content; Do_2 = oxygen delivery indexed for weight; Ket low = low-dose ketamine group; Ket high = high-dose ketamine group; Hb = hemoglobin concentration; lactate = arterial blood lactate concentration; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; O_2ER = oxygen extraction ratio; $Paco_2$ = arterial partial pressure of carbon dioxide; PAOP = pulmonary arterial occlusion pressure; pHa = arterial pH; RAP = right atrial pressure; Sao_2 = arterial oxygen saturation; SI = stroke index; Svo_2 = mixed venous oxygen saturation; SVR = systemic vascular resistance; Vo_2 = oxygen consumption indexed for weight.

Discussion

Increased anesthetic depth obtained with either halothane or ketamine resulted in a decreased tolerance to acute isovolemic anemia, as reflected by an increase in critical hemoglobin, the value of hemoglobin below which $\dot{V}o_2$ becomes supply dependent. With both agents, the increase in critical hemoglobin at the higher anesthetic level was related to a complete blunting of the CO response usually observed during isovolemic hemodilution.[1–3] Indeed, CI and SI increased only with the lower dose of each agent but not with the higher one.

These results were observed with two anesthetic agents having quite different cardiovascular properties.[17–21] The blunting of the CO response with the higher halothane concentration occurred in the presence of higher filling pressures and, despite a lower SVR, reflecting the negative inotropic properties of this agent. A depressant effect of halothane on the sympathetic system could also be implicated.[26,27] In the ketamine

Table 4. Data at Critical Point in the Ketamine Groups

	Ket low	Ket high
Do_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	8.3 ± 1.1	6.5 ± 1.3*
Vo_2 ($ml \cdot min^{-1} \cdot kg^{-1}$)	5.9 ± 0.9	4.3 ± 1.1*
O_2Er (%)	72.2 ± 9.7	66.8 ± 8.7
Do_2 from lactate ($ml \cdot min^{-1} \cdot kg^{-1}$)	10.6 ± 3.1	6.4 ± 2.0*
Lactate (mM^{-1})	1.5 ± 0.3	1.8 ± 0.5
Hb from Vo_2 ($g \cdot dl^{-1}$)	2.5 ± 0.6	3.7 ± 1.4*
Hb from lactate ($g \cdot dl^{-1}$)	2.7 ± 0.6	3.6 ± 1.7

Data are expressed as mean ± SD.

* $P < 0.05$ *vs.* Ket low.

Do_2 = oxygen delivery indexed for weight; Do_2 from lactate = oxygen delivery indexed for weight obtained from lactate measurements; Ket low = low-dose ketamine group; Ket high = high-dose ketamine group; Hb from lactate = hemoglobin concentration obtained from lactate measurements; Hb from Vo_2 = hemoglobin concentration obtained from Vo_2 measurements; O_2ER = oxygen extraction ratio; Vo_2 = oxygen consumption indexed for weight.

study, the blunting of the CO response with the higher anesthetic dosage also seemed to be related to a direct depression of the myocardial function, as reflected by the lower left ventricular stroke work index. This phenomenon occurred despite the effects of this agent on the sympathetic system, as evident from the better maintenance of MAP and SVR during the progressive hemodilution. Although ketamine possesses cardiostimulatory effects through an increase in sympathetic outflow, it also presents direct myocardial depressant properties.[28,29] In conditions associated with increased sympathetic stimulation, the direct effects of ketamine on the myocardium could exceed its sympathomimetic properties, resulting in global depressant hemodynamic effects.[30,31]

Our results may have been affected by the concomitant use of other agents such as thiopental and pancuronium. Thiopental, however, was used only in the halothane study and was administered at least 2 h before the experimental protocol. Therefore, it seems unlikely that this drug would have influenced our observations. Pancuronium was used to facilitate mechanical ventilation. This agent, which decreases vagolytic tone and increases sympathetic tone,[32] could have different effects on animals anesthetized with halothane or with ketamine. However, within each anesthetic study, it probably had little influence on our results, as the dose of muscle relaxant used was similar in animals receiving the low and the high anesthetic dosages.

Medium-molecular-weight hydroxyethyl starch was used for the hemodilution protocol as this kind of solution has been shown to produce stable plasma volume expansion.[33] Because of the high chloride concentration in the diluent of the solution, its uses may be associated with the development of metabolic acidosis, as reflected by the decrease in arterial pH observed in both the halothane and the ketamine studies. This effect, however, was similar in animals receiving the low and the high anesthetic dosages.

In this protocol of progressive hemodilution, with both agents, critical $D\dot{o}_2$ was significantly lower in the animals receiving the higher anesthetic dosage. This resulted from lower oxygen requirements as indicated by a lower critical $\dot{V}o_2$. This could be in part related to the dose-dependent negative inotropic properties of halothane and ketamine, resulting in a decreased myocardial oxygen demand. Central body temperature tended to be lower in the animal receiving the higher anesthetic dosage, despite the use of warming blankets and humidified heated gases, A difference in less than 1° in central temperature, however, could hardly explain the marked difference in oxygen consumption between the two anesthetic dosages in the halothane and ketamine studies. Indeed, hypothermia decreases whole body metabolic rate by approximately 8% by Celsius degrees.[34] The lower central body temperature observed in the animals receiving the higher anesthetic dosage could be a result of the decreased perfusion but could also reflect the effects of anesthesia on the body's thermoregulation system in a cold operating room environment.[35]

During the hemodilution protocol, $D\dot{o}_2$ decreased progressively in both the halothane and the ketamine studies as a result of the blunting of the CO response in our anesthetized animals (fig. 3). This is in contrast with previous works reporting that when hematocrit is reduced, systemic oxygen transport capacity first increases slightly, reaches a peak at approximately 30% hematocrit, and does not fall below control levels as long as the hematocrit remains above 20%.[36,37] The $D\dot{o}_2$ response to hemodilution could have been predicted with halothane but was more surprising for ketamine. This agent has a dual effect on the cardiovascular system, the balance of its indirect stimulant properties and the direct myocardial depressant properties being altered by concentration and time as shown in figure 3.

We took a number of precautions to ensure the validity of our observations. $\dot{V}o_2$ was determined from expired gas analysis, whereas $D\dot{o}_2$ was calculated from thermodilution CO and blood gas analysis, so that there was no mathematical coupling of the data. A similar protocol has been used by Cain *et al.*[9] in evaluating the effects of isovolemic anemia on critical $D\dot{o}_2$ in pentobarbital-anesthetized dogs. Determining critical $D\dot{o}_2$ "by eye," this author evaluated that the hematocrit value for which $\dot{V}o_2$ became $D\dot{o}_2$-dependent was around 10%. In the current study, critical hemoglobin was obtained from both $\dot{V}o_2$ and lactate determinations. Both approaches demonstrated similar hemoglobin values that were consistently larger in dogs anesthetized with the higher anesthetic dosage. Interestingly, critical $D\dot{o}_2$ and critical hemoglobin values obtained from lactate measurements were in agreement with those derived from $\dot{V}o_2$ measurements, confirming the usefulness of this parameter to detect the development of tissue hypoxia during profound anemia.[10,11,38]

To test the hypothesis that anesthesia can decrease tolerance to acute isovolemic hemodilution, we used two anesthetic agents with well-defined cardiovascular and metabolic effects. In the current study, when the depth of anesthesia was increased, the depressant effects of halothane and ketamine on the cardiovascular system outweighed their possible beneficial effects on tissue metabolism, whatever their effects on the sympathetic system. Our observations may not be directly applicable to other inhaled anesthetics, especially desflurane. However, newer halogenated anesthetics also have negative inotropic properties[39,40] that can decrease the CO response associated with acute isovolemic hemodilution. Although isoflurane has been shown to maintain CO better than halothane, Schou *et al.*[41] demonstrated in the pig that isoflurane induced a dose-dependent decrease in CO response during profound normovolemic hemodilu-

tion. Several studies using fentanyl–isoflurane–N_2O,[42] fentanyl–droperidol–N_2O,[43] or fentanyl–midazolam[44] anesthetic-based protocols also reported a blunting of the CO response during isovolemic hemodilution in man. A parasympathetic stimulation related to the central vagal stimulation induced by some opioids such as fentanyl[45] could be responsible for a lack of increase in HR, thereby contributing to a decrease in the CO response. Therefore, a decreased tolerance to acute isovolemic anemia when anesthesia is deepened could be relevant for other anesthetic agents with cardiovascular depressant properties. Our observations emphasize the importance of carefully titrating the level of anesthesia and monitoring the cardiovascular response in patients with moderate to severe anemia.

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