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Circulatory Effects of Hypoxia, Acute Normovolemic Hemodilution, and Their Combination in Anesthetized Pigs

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Background: **Because hemodilution decreases the oxygen-carrying capacity of blood, it was hypothesized that severe hemodilution would decrease the tolerance to alveolar hypoxia.**

Methods: **Hemodynamics, oxygen transport, and blood lactate concentrations were compared in ten pigs with normal hematocrit (33 ± 4%), and ten hemodiluted pigs (hematocrit 11 ± 1%; mean ± SD) anesthetized with ketamine-fentanyl-pancuronium during stepwise decreases in inspired oxygen fraction ($F_{I_{O_2}}$; 1.0, 0.35, 0.21, 0.15, 0.10, 0.05).**

Results: **Median systemic oxygen delivery (DO_2SY) became critical (the DO_2SY value when arterial lactate exceeded 2.0 $mmol \cdot l^{-1}$) at 10.4 $ml \cdot kg^{-1} \cdot min^{-1}$ (range 6.9–16.1) in hemodiluted animals and at 11.8 $ml \cdot kg^{-1} \cdot min^{-1}$ (5.9–32.2) in animals with normal hematocrits (NS). The relationship between mixed venous oxygen saturation and arterial lactate values was less consistent and median critical mixed venous oxygen saturation was higher ($P < 0.05$) in the hemodiluted group (35%, range 21–64), than in animals with normal hematocrits (21%, 7–68%). In animals with normal hematocrit, decreasing $F_{I_{O_2}}$ from 1.0 to 0.10 resulted in a decrease in DO_2SY from 26.3 ± 9.1 to 9.3 ± 3.9 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$). Cardiac output did not change, systemic oxygen extraction ratio increased from 0.23 ± 0.08 to 0.68 ± 0.13 ($P < 0.01$), and arterial lactate from 0.9 ± 0.2 to 3.4 ± 3.0 $mmol \cdot l^{-1}$ ($P < 0.05$). Cardiac venous blood flow, as measured by retrograde thermodilution, increased from 5.7 ± 2.9 to 12.6 ± 5.7 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$). When $F_{I_{O_2}}$ was reduced to 0.05, three animals became hypotensive and died. In the second group, hemodilution increased cardiac output and systemic oxygen extraction ratio ($P < 0.01$). Cardiac venous blood flow increased from 4.1 ± 1.7 to 9.8 ± 5.1 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$), and cardiac venous oxygen saturation from 22 ± 5 to 41 ± 10% ($P < 0.01$). During the subsequent hypoxia, cardiac output and DO_2SY were maintained until $F_{I_{O_2}} = 0.15$ ($DO_2SY = 10.1 \pm 3.3$ $ml \cdot kg^{-1} \cdot min^{-1}$). Cardiac venous blood flow was then 18.5 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$), but in spite of this, myocardial lactate production occurred. At $F_{I_{O_2}} = 0.10$ ($DO_2SY = 7.7 \pm 3.0$ $ml \cdot kg^{-1} \cdot min^{-1}$), arterial lactate concentration increased to 8.5 ± 2.3 $mmol \cdot l^{-1}$ ($P < 0.01$), and most animals became hypotensive. All hemodiluted animals died when $F_{I_{O_2}}$ was decreased to 0.05 ($P < 0.01$ when compared to animals with normal hematocrit).**

Conclusions: **Systemic and myocardial lactate production occurred at similar systemic oxygen delivery rates in hemodiluted and nonhemodiluted animals. Mixed venous oxygen saturation may be a less reliable indicator of inadequate oxygen delivery during hemodilution. (Key words: Blood, hemodilution: lactate; oxygen consumption. Heart: coronary artery blood flow. Oxygen: hypoxia.)**

THE risk of transmitting disease by allogenic blood transfusion has promoted an interest in acute normovolemic hemodilution during surgical procedures. Although the hematocrit is usually kept above 25%, values of 15–18% have been reported, and otherwise healthy children may tolerate intraoperative hemoglobin concentrations of 30 ± 9 $g \cdot l^{-1}$ (hematocrit 9%) without signs of tissue hypoxia.[1–5] During hemodilution, the decrease in hemoglobin concentration, and the concomitant decrease in oxygen-carrying capacity, is partially compensated for by increases in blood flow and oxygen extraction.[6–9] Anemia does, however, infringe on physiologic margins—marked hypotension, for example, is associated with an increased risk for cerebral anoxic damage when occurring during severe hemodilution.[10]

Cain studied the effect of anemia and hypoxia separately in dogs, and found a critical oxygen delivery value of 9.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in both groups, corresponding to a hematocrit of 10% or an inspired oxygen fraction ($F_{I_{O_2}}$) of 0.09,[11] but the effects of hypoxia and hemodilution combined has not been reported previously. The current study was designed to assess the

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cardiac and systemic response to progressive arterial desaturation in severely hemodiluted pigs without coronary artery disease. Our main objective was to clarify to what extent the tolerance to hypoxia is affected by hemodilution. We hypothesized that pigs exposed to severe hemodilution would show decreased tolerance to hypoxia, when judged by systemic oxygen uptake and arterial lactate concentration.

Materials and Methods

Animal Preparation

After approval of the local Animal Investigations Committee, 20 Swedish landrace pigs (weighing 33.7 ± 4.2 kg) were studied. The pig was chosen because its cardiovascular anatomy and physiology is similar to that of humans.[12–14] The animals were fasted overnight but had free access to water. They were premedicated with 15 mg intramuscular midazolam and anesthesia was induced with 7–10 $mg \cdot kg^{-1}$ intravenous thiopental, and 1–2 $mg \cdot kg^{-1}$ intravenous ketamine, and maintained with an infusion of 5 $mg \cdot kg^{-1} \cdot h^{-1}$ ketamine, 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl, and 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ pancuronium. Additional fentanyl (10 $\mu g \cdot kg^{-1}$) and local lidocaine were administered before insertion of central catheters.

A cuffed endotracheal tube was placed through a tracheostomy, and the lungs were mechanically ventilated with a Servo 900 ventilator (Siemens-Elema, Sweden) initially set to deliver an $F_{I_{O_2}}$ of 0.35, a respiratory rate of 20 breaths/min, and 5 cm H_2O of positive end-expiratory pressure.

Inspired oxygen fraction was measured with a Servo Gas Monitor 910 (Siemens-Elema) that had been calibrated with a series of precise oxygen-nitrogen mixtures. End-tidal CO_2 monitoring (Servo gas monitor 930, Siemens-Elema) and intermittent blood gases were used to adjust ventilation so that arterial carbon dioxide tension was 34–38 mmHg. Core temperature was maintained in the normal range (in pigs 38.5–39.5°C) with blankets and a heat-reflecting foil. Ringers' acetate, to which 20 g glucose was added per liter, was infused intravenously at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$, and a bladder catheter was inserted *via* a cystostomy.

Catheters were placed in the cranial caval vein for the administration of anesthetics and blood replacement, and in the left carotid and pulmonary arteries (thermodilution catheter, Abbott Laboratories, Illinois) for blood sampling, and measurements of blood pressure and cardiac output. A catheter with a tip-transducer (Millar Instruments, Houston, Texas) was placed in the left ventricle *via* the superficial femoral artery, to measure left ventricular pressure. Its time derivative was obtained electronically. Finally, a thermistor catheter (Webster Laboratories, California) was placed for measurements of cardiac venous flow and for sampling of blood. The catheter tip was positioned in the great cardiac vein, 3–5 cm upstream of its confluence with the azygos vein.

Catheters were inserted through peripheral cut-downs and their positions were confirmed by fluoroscopy. Catheter position in the great cardiac vein was also verified by aspirating blood with a hemoglobin oxygen saturation of approximately 25%. Occasional ventricular arrhythmia during catheter placement was treated with intravenous lidocaine. With the exception of the left ventricular pressure, pressures were measured by fluid transmission and Hewlett-Packard HP 1290 transducers. The pressures and the time derivative curve were recorded on an inkjet recorder (Mingograph 7, Siemens-Elema), with a flat frequency response up to 80 Hz.

Measurements

Cardiac output was measured in triplicate by thermodilution, using 10-ml injectates of ice-cold isotonic glucose. Flow in the great cardiac vein that mainly drains the left ventricle,[15] was measured by continuous retrograde thermodilution as described by Ganz *et al.*[16] A CF-300 flow meter (Webster Laboratories) was used. This technique has a good reproducibility if the flow rate of the indicator is sufficiently high and the catheter is not dislocated between measurements.[16] We therefore used a constant rate infusion pump (Sage 351, Orion Research, Cambridge, MA) delivering 54 $ml \cdot min^{-1}$ of isotonic saline at room temperature over approximately 20 seconds, and fixed the catheter with a ligature at its entrance into the external jugular vein. The temperature of the indicator, and that of blood in the great cardiac vein, was used to calculate cardiac venous flow (see later). Corrections were not made for possible underestimation of flow caused by thermoconductivity within the catheter.[17]

Blood samples were drawn simultaneously from the carotid artery, the pulmonary artery, and the great cardiac vein, and analyzed at 37°C for partial pressure of oxygen, partial pressure of carbon dioxide, and *p*H (ABL 30, Radiometer, Denmark). Hemoglobin concentration and oxygen saturation were obtained spectrophoto-

metrically (OSM 3 hemoxymeter, Radiometer, Denmark). The arterial hematocrit was obtained with a microhematocrit centrifuge (Hettich, Germany). Arterial and cardiac venous blood samples were frozen in liquid nitrogen and stored at −80°C for later analysis of lactate concentrations by an enzymatic-fluorometric method.[18]

Calculations

Flow in the great cardiac vein ($ml \cdot min^{-1}$) was calculated assuming that heat lost from the indicator was gained by blood[16] as:

$$F_{GCV} = F_I \cdot 1.08 \cdot ((T_M - T_I):(T_B - T_M) - 1),$$

where F_I indicates indicator flow, and T the temperature of indicator (I), blood (B), and the indicator and blood mixture (M), respectively. The value 1.08 is the relationship between the density (S) and the specific heat (C) of blood and indicator($(S_I \cdot C_I):(S_B \cdot C_B)$).

The oxygen content of blood, $ml \cdot l^{-1}$, was obtained from:

$$C_xO_2 = =Hb \cdot 1.39 \cdot S_xO_2 + 0.03 \cdot P_xO_2$$

where x denotes arterial (a), great cardiac venous (GCV), or mixed venous (v) blood.

Systemic and myocardial (left ventricular) oxygen delivery, $ml \cdot min^{-1}$, were calculated as:

$$DO_2SY = CO \cdot Ca_{O_2} \text{ and } DO_2LV = F_{GCV} \cdot Ca_{O_2}$$

and systemic and myocardial (left ventricular) oxygen uptake, $ml \cdot min^{-1}$, as:

$$VO_2SY = CO \cdot (CaO_2 - C_VO_2)$$

$$\text{and } VO_2LV = F_{GCV} \cdot (CaO_2 - C_{GCV}O_2)$$

These values, including F_{GCV}, were indexed to body weight.

Systemic and myocardial (left ventricular) oxygen extraction ratio were calculated as:

$$ER_{SY} = VO_2SY:DO_2 \text{ and } ER_{LV} = VO_2LV:DO_2LV$$

The values for systemic oxygen delivery and mixed venous oxygen saturation, respectively, at which an arterial lactate of 2 $mmol \cdot l^{-1}$ was exceeded (defined as critical systemic oxygen delivery and critical Sv_{O_2}), was determined in each animal by linear interpolation. The cutoff value of 2 $mmol \cdot l^{-1}$ was the mean baseline value +2 SD. In three animals with normal hematocrit, this threshold was not exceeded even at $FI_{O_2} = 0.10$. In these, critical oxygen delivery and critical Sv_{O_2} were approximated as the measured values at $FI_{O_2} = 0.10$ (lactate concentrations were not measured at $FI_{O_2} = 0.05$ because of technical problems). The estimates (8, 14, and 16 $ml \cdot kg^{-1} \cdot min^{-1}$ for systemic oxygen delivery, and 16, 21, and 31% for mixed venous oxygen saturation) were thus an unknown amount above the true critical value.

Experimental Protocol

After preparation, which lasted 60–90 min, the animals were left undisturbed for at least 45 min. Inspired oxygen fraction was then increased from 0.35 to 1.0 and after waiting 10 min to achieve steady state, baseline measurements were obtained. The animals were then assigned randomly to either of two groups of ten animals each. One group (weight 32 ± 4 kg) was immediately exposed to decreasing FI_{O_2} (see later), while the other group (weight 35 ± 4 kg) was first hemodiluted. To ensure that systemic oxygen delivery would be reduced to a critical level (*i.e.,* to about 10 $ml \cdot kg^{-1} \cdot min^{-1}$), the hematocrit was reduced to 11%.[11,19]

Hemodilution was performed by removing blood from the arterial catheter, and simultaneously replacing this with a warmed (38°C) 1:1 mixture of 6% dextran-70 (Pharmacia, Sweden) and Ringers' acetate. A similar mixture (3% dextran-60) gives isovolemic plasma expansion in man.[20] Each liter of the mixture contained: Na^+ 142 mM, K^+ 1 mM, Cl^- 132 mM, Ca^{++} 1 mM, Mg^{++} 0.5 mM, acetate 15 mM, and dextran-70 30 g. The exchanged volume (mean ± SD) to achieve a hematocrit of 11 ± 1% was 66 ± 10 $ml \cdot kg^{-1}$ (range, 48–78 $ml \cdot kg^{-1}$). Because the hemodilution procedure took approximately 1 h, the two groups were not time-matched. Ten minutes after completing the hemodilution, new measurements were performed at $FI_{O_2} = 1.0$.

The hypoxic challenge was accomplished through a stepwise reduction in FI_{O_2}: 1.0 − 0.35 − 0.21 − 0.15 − 0.10 − 0.05. Measurements and blood samples were performed at each level after 10 min at constant FI_{O_2}. Because adjusting the oxygen concentration to a smaller value usually took 5 min, and the measurements about 15 min, the pigs were exposed to each FI_{O_2} for approximately 30 min. At $FI_{O_2} = 0.05$, many animals became hemodynamically unstable and measurements therefore could only be obtained in seven animals, all with normal hematocrits. Animals that were still alive after 30 min of ventilation at $FI_{O_2} = 0.05$, were killed by an intravenous bolus of thiopental.

Statistics

Two-way (group and stage) analysis of variance with repeated measures was applied for continuous

variables (saturation, F_{GCV}, *etc.*), to determine whether there was any significant overall group effect or interaction between group and stage. If so, possible differences between groups at specific stages were analyzed with the two-sided *t* test for unpaired data. Changes between baseline and the following stages, within groups, were similarly assessed with one-way analysis of variance and the two-sided *t* test for paired data. Group differences in critical systemic oxygen delivery and Sv_{O_2} were assessed by a generalization of Mann-Whitney's rank sum test. Fisher's exact test was used to assess whether mortality differed between groups. Probability values less than 0.05 were considered significant. Data are reported as mean ± SD when not otherwise indicated.

Results

Critical Systemic Oxygen Delivery and Critical Mixed Venous Oxygen Saturation

Arterial lactate levels and systemic oxygen delivery were closely related (fig. 1). In hemodiluted animals, systemic oxygen delivery became critical when less than 10.4 (6.9–16.1) $ml \cdot kg^{-1} \cdot min^{-1}$ (median and range). This was not significantly different from the value of 11.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in the group with normal hematocrit (5.9–32.5 $ml \cdot kg^{-1} \cdot min^{-1}$). As mentioned in the section titled Calculations, the value for critical DO_{2SY} was approximated in three animals in the control group by a figure that was an unknown amount above the true critical value, but even if one makes the unrealistic assumption that the true DO_{2SY} values in these three pigs were also the smallest ones of the entire material, this would give a median value of 8.75 $ml \cdot kg^{-1} \cdot min^{-1}$, still not significantly different from that of the hemodiluted animals.

The relationship between arterial lactate levels and SV_{O_2} was less consistent (fig. 1). Median critical Sv_{O_2} was 35% (range 21–64%) in hemodiluted animals, and 21% (range 7–68%) in animals with normal hematocrits ($P < 0.05$). As concerns the Sv_{O_2} approximations, the between-group difference would have been even larger if critical DO_{2SY} values had been determined in all animals with normal hematocrits.

Effects of Decreasing Inspired Oxygen Fraction in Animals with Normal Hematocrits

Systemic Circulation and Oxygenation. The decrease in arterial oxygen content occurring during the hypoxic challenge, was predominantly compensated for by an increase in systemic oxygen extraction ratio. Except for an increase in mean pulmonary arterial pressure ($P < 0.01$) and pulmonary vascular resistance ($P < 0.01$), only minor hemodynamic changes were observed as long as FI_{O_2} was greater than 0.10 (tables 1 and 2). At $FI_{O_2} = 0.10$ ($Sa_{O_2} = 38 \pm 11\%$), systemic

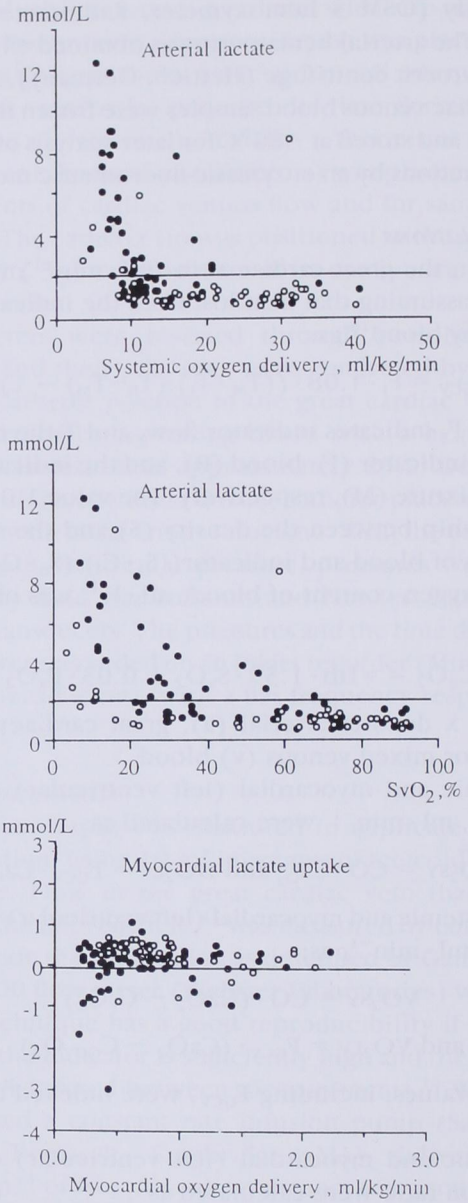

Fig. 1. Arterial lactate and myocardial lactate uptake (arterial minus cardiac venous lactate concentration) *versus* systemic oxygen delivery, and arterial lactate *versus* mixed venous oxygen saturation in hemodiluted animals (●) and in animals with normal hematocrit (○).

Table 1. Systemic and Pulmonary Circulation

		$F_{I_{O_2}}$						
		1.0	1.0	0.35	0.21	0.15	0.10	0.05
Hematocrit (%)	NO	—	33 ± 3	33 ± 3	32 ± 3	33 ± 4	34 ± 3	40 ± 5§
	HD	33 ± 4	11 ± 1†·**	11 ± 2**	12 ± 2§·**	14 ± 2§·**	15 ± 1§·**	—
Hemoglobin (g/l)	NO	—	105 ± 11	103 ± 10	102 ± 11	105 ± 12	107 ± 12	121 ± 16§
	HD	105 ± 13	33 ± 5†·**	35 ± 6‡·**	39 ± 5§·**	44 ± 5§·**	48 ± 4§·**	—
MAP (mmHg)	NO	—	147 ± 18	146 ± 15	147 ± 17	142 ± 13	121 ± 28‡	107 ± 14§
	HD	151 ± 16	133 ± 18*	123 ± 17**	119 ± 17‡·**	100 ± 25§·**	86 ± 27§·¶	—
HR (beats/min)	NO	—	111 ± 21	116 ± 25	120 ± 23‡	133 ± 25§	150 ± 26§	170 ± 21§
	HD	122 ± 19	144 ± 33*·¶	160 ± 28§·**	167 ± 28§·**	170 ± 25§·**	167 ± 27§	—
CO ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO		168 ± 64	172 ± 72	169 ± 60	173 ± 58	193 ± 56	136 ± 44‡
	ND	171 ± 64	212 ± 52†	221 ± 42	223 ± 35¶	218 ± 43	171 ± 54‡	—
SV (ml/beat)	NO	—	46.8 ± 11.4	46.2 ± 15.0	44.7 ± 13.1	40.8 ± 7.4‡	41.2 ± 8.8	24.9 ± 7.0§
	HD	47.8 ± 12.1	52.7 ± 11.2	49.6 ± 11.9‡	48.0 ± 11.4‡	45.4 ± 9.1‡	36.9 ± 13.5§	—
CVP (mmHg)	NO	—	1.9 ± 1.4	2.4 ± 1.3	2.8 ± 1.1§	3.2 ± 1.9	3.3 ± 2.8	5.6 ± 1.3§
	HD	2.8 ± 1.1	2.4 ± 1.5	3.3 ± 1.9	3.5 ± 1.9§	5.0 ± 2.0§·¶	6.2 ± 2.2§·**	—
MPAP (mmHg)	NO	—	19.3 ± 7.3	24.1 ± 11.6	27.7 ± 14.0§	31.5 ± 12.9§	34.3 ± 8.9§	30.4 ± 6.6§
	HD	20.7 ± 4.0	20.9 ± 6.2	21.2 ± 5.9	22.3 ± 5.6	27.5 ± 7.9‡	29.5 ± 11.6‡	—
PCWP (mmHg)	NO	—	5.4 ± 2.0	5.0 ± 1.9	6.3 ± 2.9	5.4 ± 2.0	5.9 ± 2.3§	15 ± 4§
	HD	6.3 ± 2.5	5.5 ± 2.4	5.9 ± 2.0	6.4 ± 2.6	7.3 ± 2.6‡	9.6 ± 2.7§·**	—
SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$)	NO	—	31 ± 12	31 ± 18	32 ± 16	28 ± 10	19 ± 5§	26 ± 9
	HD	29 ± 12	18 ± 4†·**	16 ± 4‡·¶	15 ± 3‡·**	13 ± 3§·**	14 ± 4‡·¶	—
PVR ($mmHg \cdot l^{-1} \cdot min^{-1}$)	NO	—	3.2 ± 2.4	3.9 ± 3.2	5.0 ± 4.0‡	5.8 ± 3.9§	4.6 ± 2.2	5.0 ± 2.1‡
	HD	2.9 ± 2.0	2.5 ± 1.1	2.2 ± 1.0	2.1 ± 0.9¶	2.7 ± 1.4¶	3.4 ± 1.5	—
Diuresis ($ml \cdot kg^{-1}h^{-1}$)	NO		2.8 ± 2.3	2.4 ± 1.5	5.2 ± 4.4	2.9 ± 3.1	2.2 ± 2.2	5.1 ± 2.7
	HD	2.9 ± 2.5	8.0 ± 6.4*	8.2 ± 6.6¶	8.2 ± 4.8	4.6 ± 5.7	3.8 ± 3.4	

NO = normal hematocrit; HD = hemodiluted.

Data are mean ± SD.

Data obtained before hemodilution are shown in the left hand column.

* $P < 0.05$, † $P < 0.01$ *versus* before hemodilution (column 1 *vs.* column 2); ‡ $P < 0.05$, § $P < 0.01$ *versus* $F_{I_{O_2}} = 1.0$ (column 2 *vs.* columns 3–7); and ¶ $P < 0.05$, ** $P < 0.01$ *versus* the corresponding stage in NO animals.

Table 2. Systemic and Pulmonary Oxygenation

		$F_{I_{O_2}}$						
		1.0	1.0	0.35	0.21	0.15	0.10	0.05
Hematocrit (%)	NO	—	33 ± 3	33 ± 3	32 ± 3	33 ± 4	34 ± 3	40 ± 5§
	HD	33 ± 4	11 ± 1†,**	11 ± 2**	12 ± 2§,**	14 ± 2§,**	15 ± 1§,**	—
Pa_{O_2} (mmHg)	NO	—	474 ± 47	149 ± 23§	80 ± 16§	52 ± 11§	25 ± 6§	18 ± 3§
	HD	431 ± 86	458 ± 77*	128 ± 36§	73 ± 21§	45 ± 8§	35 ± 6§,**	—
Sa_{O_2} (%)	NO	—	100	99.7 ± 0.3§	96 ± 3§	78 ± 21‡	38 ± 11§	15 ± 3§
	HD	100	100	98.8 ± 2.0	93 ± 7‡	72 ± 16§	51 ± 9§,¶	—
Sv_{O_2} (%)	NO	—	83 ± 8	70 ± 9§	63 ± 9§	46 ± 21§	13 ± 8§	5 ± 1§
	HD	81 ± 11	65 ± 11†,**	39 ± 12§,**	32 ± 9§,**	22 ± 12§,**	13 ± 6§	—
La (mM)	NO	—	0.9 ± 0.2	0.9 ± 0.3	1.0 ± 0.3‡	1.9 ± 2.5	3.4 ± 3.0‡	—
	HD	1.1 ± 0.4	1.5 ± 0.8¶	1.8 ± 1.0‡,**	2.3 ± 1.1§,**	4.2 ± 2.1§,¶	8.5 ± 2.3§,**	—
*p*H	NO	—	7.47 ± 0.04	7.49 ± 0.04‡	7.50 ± 0.04§	7.47 ± 0.08	7.44 ± 0.08	7.26 ± 0.07§
	HD	7.48 ± 0.05	7.45 ± 0.03	7.47 ± 0.03‡	7.48 ± 0.04	7.44 ± 0.10	7.33 ± 0.15‡	—
Pa_{CO_2} (mmHg)	NO	—	36.3 ± 3.4	35.3 ± 3.4	34.7 ± 3.3§	34.5 ± 3.7‡	37.9 ± 3.6	33.3 ± 4.3
	HD	37.2 ± 3.2	38.4 ± 2.9	36.5 ± 4.8	34.5 ± 2.1‡	36.6 ± 4.5	34.4 ± 2.8§,**	
ABE (mM)	NO	—	3.5 ± 1.4	3.7 ± 1.1	4.0 ± 1.1§	3.5 ± 1.2	1.4 ± 4.1	−10.7 ± 4.2§
	HD	3.3 ± 1.3	2.7 ± 2.0	3.1 ± 2.3	2.7 ± 2.5	−0.14 ± 5.0‡,¶	−7.3 ± 6.6§,**	
O_2 content (ml/l)	NE	—	160 ± 15	147 ± 14§	139 ± 15§	115 ± 33§	56 ± 15§	25 ± 3§
	HD	158 ± 19	60 ± 7†,**	52 ± 8§,**	52 ± 6§,**	45 ± 9§,**	35 ± 6§,**	—
DO_{2SY} ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO	—	26.3 ± 9.1	24.2 ± 8.2§	23.4 ± 9.1	19.0 ± 8.6§	9.3 ± 3.9§	3.6 ± 1.4§
	HD	26.3 ± 8.3	11.5 ± 3.9†,**	11.2 ± 4.0**	11.6 ± 4.0**	10.1 ± 3.3**	7.7 ± 3.0§	—
VO_{2SY} ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO	—	5.4 ± 1.0	7.3 ± 1.6§	7.1 ± 1.7§	7.8 ± 2.5‡	6.6 ± 1.5‡	2.3 ± 1.1§
	HD	5.8 ± 1.1	5.6 ± 1.6	6.7 ± 0.7	7.5 ± 0.7§	6.8 ± 1.5‡	4.4 ± 2.0¶	—
ER_{SY}	NO	—	0.23 ± 0.08	0.32 ± 0.07§	0.35 ± 0.09§	0.48 ± 0.15§	0.68 ± 0.13§	0.66 ± 0.13§
	HD	0.24 ± 0.09	0.45 ± 0.08†,**	0.60 ± 0.12‡,**	0.66 ± 0.09§,**	0.71 ± 0.10§,**	0.74 ± 0.09§	—

NO = normal hematocrit; HD = hemodiluted.

Data are mean ± SD.

Data obtained before hemodilution are shown in the left hand column.

* $P < 0.05$, † $P < 0.01$ *versus* before hemodilution (column 1 *vs.* column 2); ‡ $P < 0.05$, § $P < 0.01$ *versus* $F_{I_{O_2}} = 1.0$ (column 2 *vs.* columns 3–7); and ¶ $P < 0.05$, ** $P < 0.01$ *versus* the corresponding stage in NO animals.

oxygen delivery had decreased to 9.3 ± 3.9 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$) and arterial lactate increased to 3.4 ± 3.0 $mmol \cdot l^{-1}$ ($P < 0.05$), in spite of a maintained systemic oxygen uptake.

When $F_{I_{O_2}}$ was further decreased to 0.05 (Sa_{O_2} = 15 ± 3%, systemic oxygen delivery = 3.6 ± 1.4 $ml \cdot kg^{-1} \cdot min^{-1}$) the decreased arterial oxygen content was not compensated for by further increases in oxygen extraction and the animals showed signs of progressive circulatory failure with decreases in cardiac output and increasing mean central venous pressure and pulmonary capillary wedge pressure. Three pigs developed severe hypotension and bradycardia and died, two of these had shown markedly increased arterial lactate levels at $F_{I_{O_2}}$ = 0.10. In the remaining seven animals, arterial pressure and cardiac output decreased and heart rate and wedge-pressure increased, but all survived 30 min at $F_{I_{O_2}}$ = 0.05.

Myocardial Hemodynamics and Oxygenation. There was no myocardial lactate production during the decrease in $F_{I_{O_2}}$ from 1.0 to 0.15 (table 3). Left ventricular time derivative increased and the oxygen requirements of the heart were met by an increase in coronary blood flow. Although the cardiac venous oxygen saturation decreased, the oxygen extraction ratio was unchanged. When $F_{I_{O_2}}$ was decreased from 0.15 to 0.10, myocardial lactate production was observed. At $F_{I_{O_2}}$ = 0.05 myocardial oxygen delivery decreased from 0.65 ± 0.37 to 0.30 ± 0.16 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$).

Acute Normovolemic Hemodilution at Inspired Oxygen Fraction of 1.0

Systemic Circulation and Oxygenation. Following hemodilution from hematocrit 33 to 11% there was a 56% decrease in systemic oxygen delivery ($P < 0.01$). Mixed venous oxygen saturation decreased ($P < 0.01$), and the systemic oxygen extraction ratio increased from 0.24 ± 0.09 to 0.45 ± 0.08 ($P < 0.01$), but there were no changes in arterial lactate concentration, systemic oxygen uptake, or *p*H (fig. 2 and tables 1 and 2). Mean arterial pressure and systemic vascular resistance decreased by 12 and 38% ($P < 0.05$ and $P < 0.01$, respectively), and cardiac output increased by 24% ($P < 0.01$).

Myocardial Hemodynamics and Oxygenation. Cardiac venous blood flow increased by 140% after hemodilution ($P < 0.01$). Myocardial oxygen delivery and uptake were unchanged (table 3). Cardiac venous oxygen saturation increased from 22 ± 5% to 41 ± 10% ($P < 0.01$), and the oxygen extraction ratio of the myocardium decreased from 0.79 ± 0.04 to 0.67 ± 0.08 ($P < 0.01$). Myocardial lactate uptake was unaffected (fig. 2).

Effects of Decreasing Inspired Oxygen Fraction in Hemodiluted Animals

Systemic Circulation and Oxygenation. As was the case in animals with normal hematocrit, the decrease in arterial oxygen content caused by hypoxia was mainly compensated for by an increase in systemic oxygen extraction ($P < 0.01$), but Sv_{O_2} was less than in pigs with normal hematocrit until $F_{I_{O_2}}$ = 0.10 ($p < 0.01$; tables 1 and 2). In contrast to animals with normal hematocrit, pulmonary vascular resistance did not increase in hemodiluted animals when $F_{I_{O_2}}$ was decreased, which could be owing to the low viscosity. Mean arterial pressure decreased ($P < 0.01$), largely because of a decrease in systemic vascular resistance ($P < 0.05$). At $F_{I_{O_2}}$ = 0.15 (Sa_{O_2} = 72 ± 16%) systemic oxygen delivery was maintained (10.1 ± 3.3 $ml \cdot kg^{-1} \cdot min^{-1}$), there was an increase in arterial lactate to 4.2 ± 2.1 $mmol \cdot l^{-1}$ ($P < 0.01$), and arterial base excess became negative ($P < 0.05$; table 2). At $F_{I_{O_2}}$ = 0.10 systemic oxygen delivery decreased to 7.7 ± 3.0 $ml \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$). Arterial lactate increased to 8.5 ± 2.3 $mmol \cdot L^{-1}$ ($P < 0.01$), and arterial base excess decreased further ($P < 0.01$). Simultaneously, cardiac output decreased, and central venous pressure and pulmonary capillary wedge pressure increased, indicating circulatory failure.

No animal survived ventilation with an $F_{I_{O_2}}$ of 0.05 ($P < 0.01$ compared with the animals with normal hematocrit). Eight animals died within 10 min, and the other two within 30 min. Death occurred after a period of progressive hypotension and bradycardia.

Myocardial Hemodynamics and Oxygenation. During the hypoxic challenge, flow in the great cardiac vein increased from 9.8 ± 5.1 $ml \cdot kg^{-1} \cdot min^{-1}$ at $F_{I_{O_2}}$ = 1.0 to a maximum of 18.5 ± 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$ at = 0.15 ($P < 0.01$). Myocardial blood flow remained greater in hemodiluted animals than in animals with normal hematocrit (fig. 3 and table 3), until $F_{I_{O_2}}$ was decreased to 0.10, and there continued to be a net myocardial uptake of lactate until $F_{I_{O_2}}$ = 0.15 (fig. 2). Myocardial lactate uptake *versus* myocardial oxygen delivery is given in figure 1.

Table 3. Myocardial Circulation and Oxygenation

		FI_{O_2}						
		1.0	1.0	0.35	0.21	0.15	0.10	0.05
Hematocrit (%)	NO	—	33 ± 3	33 ± 3	32 ± 3	33 ± 4	34 ± 3	40 ± 5§
	HD	33 ± 4	11 ± 1†·**	11 ± 2**	12 ± 2§·**	14 ± 2§·**	15 ± 1§·**	—
LVdP/dt (mmHg/s)	NO	—	2,920 ± 677	3,123 ± 812‡	3,180 ± 770	3,498 ± 773§	3,685 ± 1,176	2,856 ± 384
	HD	2,963 ± 551	3,878 ± 872†·¶	3,960 ± 576*·¶	4,160 ± 683‡·**	3,825 ± 825	3,345 ± 1,017	—
F_{GCV} ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO	—	5.7 ± 2.9	7.2 ± 4.9	7.6 ± 3.2‡	9.4 ± 6.6‡	12.6 ± 5.7§	11.9 ± 5.3‡
	HD	4.1 ± 1.7	9.8 ± 5.1†·¶	14.2 ± 6.6§·¶	16.1 ± 8.5§·**	18.5 ± 10.7§·¶	17.9 ± 14.1	—
$P_{GCV}O_2$ (mmHg)	NO	—	24 ± 4	20 ± 4§	19 ± 3§	16 ± 6§	10 ± 5§	5 ± 2§
	HD	22 ± 2	29 ± 5†·¶	27 ± 4**	23 ± 2‡·**	18 ± 6§	14 ± 5§	—
$S_{GCV}O_2$ (%)	NO	—	29 ± 8	24 ± 6§	24 ± 6‡	19 ± 9‡	11 ± 7§	4 ± 3§
	HD	22 ± 5	41 ± 10†·**	38 ± 7**	33 ± 6**	21 ± 9§	12 ± 6§	—
L_a-L_{GCV} (mM)	NO	—	0.31 ± 0.22	0.37 ± 0.18	0.29 ± 0.27	0.24 ± 0.41	−0.22 ± 0.95	—
	HD	0.40 ± 0.34	0.20 ± 0.18	0.22 ± 0.18	0.15 ± 0.20	−0.08 ± 0.38§	−0.93 ± 0.90§·¶	—
DO_{2Lv} ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO	—	0.89 ± 0.41	1.03 ± 0.64	1.03 ± 0.43	0.97 ± 0.60	0.65 ± 0.37	0.30 ± 0.16§
	HD	0.65 ± 0.28	0.60 ± 0.30	0.76 ± 0.44‡	0.87 ± 0.58‡	0.86 ± 0.58‡	0.64 ± 0.54	—
VO_{2Lv} ($ml \cdot kg^{-1} \cdot min^{-1}$)	NO	—	0.65 ± 0.31	0.77 ± 0.47	0.77 ± 0.33‡	0.74 ± 0.44	0.47 ± 0.25	0.25 ± 0.13§
	HD	0.51 ± 0.22	0.40 ± 0.25	0.48 ± 0.29‡	0.55 ± 0.34‡	0.59 ± 0.38§	0.51 ± 0.40	—
ER_{Lv}	NO	—	0.73 ± 0.07	0.76 ± 0.06‡	0.75 ± 0.07	0.77 ± 0.08	0.74 ± 0.12	0.78 ± 0.05
	HD	0.79 ± 0.04	0.67 ± 0.08†	0.63 ± 0.07§·**	0.65 ± 0.04**	0.69 ± 0.10	0.76 ± 0.08‡	—

NO = normal hematocrit; HD = hemodiluted.

Data are mean ± SD.

Data obtained before hemodilution are shown in the left hand column.

* $P < 0.05$, † $P < 0.01$ *versus* before hemodilution (column 1 *vs.* column 2); ‡ $P < 0.05$, § $P < 0.01$ *versus* $FI_{O_2} = 1.0$ (column 2 *vs.* columns 3–7); and ¶ $P < 0.05$, ** $P < 0.01$ *versus* the corresponding stage in NO animals.

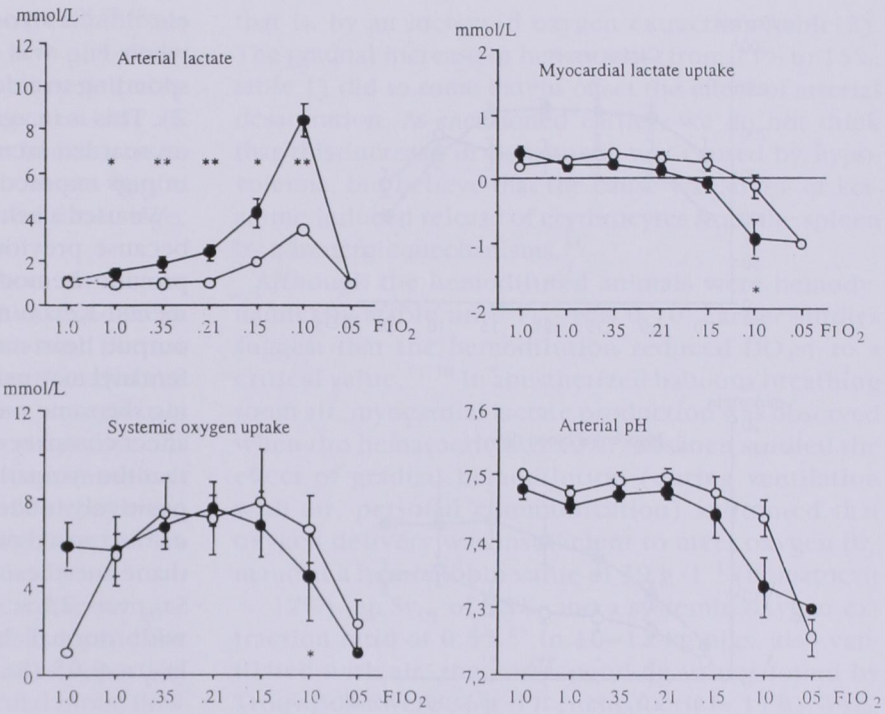

Fig. 2. Arterial lactate, myocardial lactate uptake, systemic oxygen uptake, and arterial *p*H in hemodiluted animals (●) and in animals with normal hematocrit (○). Data are mean ± SE. Significant differences between groups are indicated: *$P < 0.05$, and **$P < 0.01$.

Discussion

Critical Systemic Oxygen Delivery and Critical Mixed Venous Oxygen Saturation

The determination of critical oxygen delivery was based on arterial lactate measurements. In contrast to systemic oxygen uptake, which is mathematically coupled to oxygen delivery and Sv_{O_2}, lactate is an independent indicator of inadequate oxygen delivery. We found increased arterial lactate concentrations at similar oxygen delivery in the two groups (about 10 $ml \cdot kg^{-1} \cdot min^{-1}$, fig. 1), which suggests that the effects of hemodilution and of hypoxia were additive. This agrees with studies in dogs, in which systemic oxygen uptake decreased when systemic oxygen delivery became less than 10 $ml \cdot kg^{-1} \cdot min^{-1}$, regardless of whether the decrease in oxygen delivery was caused by anemia, hypoxia, or low cardiac output.[11,21]

A problem during clinical hemodilution is how to detect early signs of inadequate oxygen delivery. When analyzing the data obtained in our animals during the stages preceding death, it was difficult to discern a reliable indicator of impending decompensation. Although close circulatory monitoring is mandatory during hemodilution, circulatory changes are not specific and hemodynamic collapse may occur rapidly once signs of circulatory decompensation appear[21–23] and resuscitation may be difficult.[24] Lactate, standard bicarbonate, base excess and Sv_{O_2} measurements are more specific indicators of inadequate systemic oxygen delivery. Of these, Sv_{O_2} is clinically appealing because it can easily be monitored continuously. Several studies have found good correlation between oxygen uptake and Sv_{O_2} values,[25,26] but to our knowledge, no study has related Sv_{O_2} and an independent measure of tissue oxygenation (*e.g.*, lactate concentration). The usefulness of Sv_{O_2} as a monitor during hemodilution is uncertain. In a recent case report of a patient hemodiluted to a hematocrit of 8%, critical oxygen delivery, defined as the DO_2SY value below which the VO_2SY gradually decreased, was about 184 $ml \cdot m^{-2} \cdot min^{-1}$.[27] Sv_{O_2} values were not presented but Pv_{O_2} was the same (31 mmHg) before anesthetic induction and 8 h after surgery, although DO_2SY decreased from 339 to 78 $ml \cdot m^{-2} \cdot min^{-1}$.

None of our animals had increased lactate concentrations as long as Sv_{O_2} was >70%. When hypoxia was increased, however, the relationship between Sv_{O_2} and arterial lactate concentrations was different in animals that had been diluted, and those who had not (fig. 1). We have no certain explanation for the greater critical Sv_{O_2} in hemodiluted animals (35% *vs.* 21% in animals

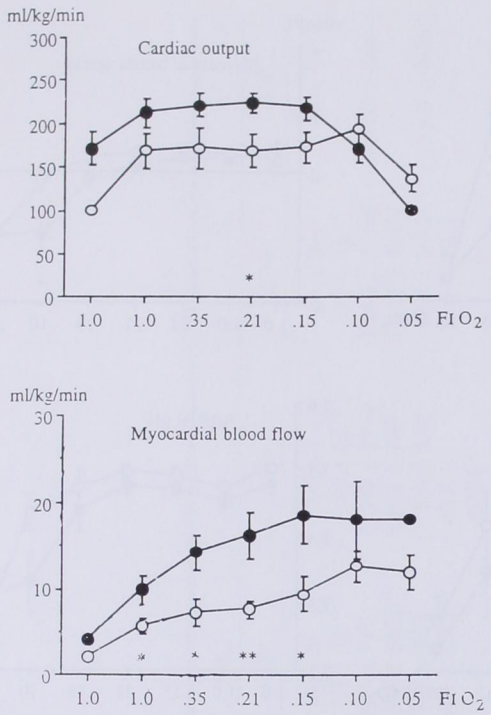

Fig. 3. Cardiac output and cardiac venous flow in hemodiluted animals (●) and in animals with normal hematocrit (○). Data are mean ± SE. Significant differences between groups are indicated: *$P < 0.05$, and **$P < 0.01$.

with normal hematocrit). A poor correlation has been demonstrated between regional venous saturation and Sv_{O_2} in hemodiluted pigs (hematocrit 15%) undergoing cardiopulmonary bypass.[28] It is possible that a low hematocrit may affect the accuracy of Sv_{O_2} determinations.

Effects of Decreasing Inspired Oxygen Fraction in Animals with Normal Hematocrit

There were no signs of circulatory decompensation when FI_{O_2} was decreased from 1.0 to 0.15. Cardiac output remained stable and the decrease in systemic oxygen delivery was compensated for by an increase in oxygen extraction. These findings confirm previous studies in dogs and lambs.[21–23,29] Increased arterial lactate concentration was observed at $FI_{O_2} = 0.10$ when oxygen delivery was 9.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (fig. 2 and table 2).

Initially during the hypoxic challenge, myocardial oxygen delivery was maintained by a more than doubled myocardial blood flow. This is consistent with earlier reports in dogs and lambs and indicates that hypoxia is a strong coronary vasodilator, perhaps because of its effect on regional *p*H and lactate levels.[23,29,30] Myocardial lactate production occurred when FI_{O_2} was decreased from 0.15 to 0.10, corresponding to a decrease in Sa_{O_2} from 78% to 38% (table 2). This is in agreement with the finding of a switch to myocardial lactate production at an Sa_{O_2} of 57% ± 5% in pigs exposed to stepwise reduction in FI_{O_2}.[24]

We used a ketamine-fentanyl-pancuronium anesthetic because previous experience indicated that it would provide hemodynamic stability during long experiments. Ketamine and pancuronium increase cardiac output, heart rate, and arterial blood pressure, whereas fentanyl may partly antagonize these effects by decreasing the same measures. Neither fentanyl nor ketamine affect coronary vascular tone in pigs.[31–33] It is possible that the sympathetic stimulation provided by ketamine positively influenced survival in both groups: White *et al.*[24] exposed pigs to progressive hypoxia during halothane anesthesia, and found that all animals died when Sa_{O_2} was 23 ± 3%, whereas seven of our ten animals with normal hematocrit survived ventilation with $FI_{O_2} = 0.05$ (Sa_{O_2} 15 ± 3%) for longer than 30 min.

Effects of Acute Normovolemic Hemodilution at Inspired Oxygen Fraction of 1.0

The anesthetic technique also may explain some other findings. Except for the anesthetic, our animal model is similar to the one used by van Woerkens *et al.* and by Räsänen.[19,25] These groups studied midazolam-fentanyl-[19] and pentobarbital-anesthetized pigs, hemodiluted to a hematocrit of 9–11% during normoxic ventilation, and found that the decrease in oxygen content was compensated for by an increase in cardiac output of 100% and 39%, respectively. In our study, cardiac output increased by 24%, but while these increase in cardiac output was mainly caused by an increase in stroke volume, ours was caused solely by an increase in heart rate (table 1).

Whereas these two groups used dextran-40 as replacement fluid during hemodilution, we used 3% dextran-70. In humans, 3% dextran-60 produces isovolemia when used to replace blood loss milliliter per milliliter.[20] In the current study, the maintained central venous pressure and wedge pressure after hemodilution suggest that hemodilution was isovolemic. The blood volume of 2–3-month old pigs is 67 ± 4 $mg \cdot kg^{-1}$, *i.e.*, almost the same as our exchanged volume (66 ± 10 $ml \cdot kg^{-1}$).[34] If one assumes exponential hemodilution, these figures imply a mean hematocrit reduction by a factor of 2.7.[3] Because the actual value was 3.0, this is consistent with isovolemic, or even slightly hyper-

volemic, blood replacement. We chose to administer a relatively large amount (10 $ml \cdot kg^{-1} \cdot h^{-1}$) of maintenance fluid, and recorded a satisfactory diuresis (table 1). The maintenance fluid does not seem to have affected the blood volume, because the hematocrit as well as the hemoglobin values were constant in the group with normal hematocrit until the final stage, when it increased.

Because of the hemodilution sequence, the hemodiluted animals were anesthetized and exposed to an $F_{I_{O_2}}$ of 1.0 for 1 h longer than the animals with normal hematocrit. In theory, this might have confounded the comparison between groups. However, the animals with normal hematocrit exhibited essentially unchanged hemodynamics and lactate concentrations during a comparable period, namely when they were exposed to $F_{I_{O_2}} = 1.0$, 0.35, and 0.21 (fig. 2 and tables 1 and 2).

In our animals, the flow in the great cardiac vein increased by 140% after hemodilution (table 3), and the current findings thus confirm earlier studies, reporting twofold to fourfold increases in myocardial blood flow as determined by ^{133}Xenon washout, electromagnetic flow probe, and microsphere techniques, during similar degrees of hemodilution.[7,10,19,25,35] The large increase in myocardial blood flow was probably the result of both decreased blood viscosity, and of *p*H- and lactate-mediated dilation of the coronary vessels, and reflect the finding that the capacity of the myocardium for increasing the oxygen extraction is limited.[7,30] It is conceivable that the acetate in our replacement solution temporarily increased coronary flow, but the vasodilatory effect of acetate lasts only 2 or 3 min, and it is therefore unlikely that the observed increase in coronary flow during the subsequent experiment was influenced by this factor.[36,37] The increase in coronary venous saturation after hemodilution (from 22% to 41%, table 3) was greater than the increase reported by Woerkens *et al.* (from 22% to 28%).[19] It occurred in the absence of myocardial lactate production, which suggests that the blood flow was sufficient to meet myocardial oxygen demand. It is possible that shunting at the capillary level accounts for at least part of the increase.

Effects of Decreasing Inspired Oxygen Fraction during Acute Normovolemic Hemodilution

In hemodiluted animals, the decrease in blood oxygen content during hypoxia was compensated for in a similar manner as in animals with normal hematocrit, that is, by an increased oxygen extraction (table 2). The gradual increase in hematocrit (from 11% to 15%; table 1) did to some extent offset the effect of arterial desaturation. As mentioned earlier, we do not think that this increase in hematocrit was caused by hypovolemia, but believe that the cause was stress- or ketamine-induced release of erythrocytes from the spleen by adrenergic mechanisms.[34]

Although the hemodiluted animals were hemodynamically stable until $F_{I_{O_2}}$ was 0.10, earlier studies suggest that the hemodilution reduced DO_{2SY} to a critical value.[11,38] In anesthetized baboons breathing room air, myocardial lactate production was observed when the hematocrit was 10%.[7] Räsänen studied the effect of gradual hemodilution (during ventilation with air, personal communication) and noted that oxygen delivery was insufficient to meet oxygen demand at a hemoglobin value of 39 $g \cdot l^{-1}$ (hematocrit $\approx$ 12%), an Sv_{O_2} of 38%, and a systemic oxygen extraction ratio of 0.55.[25] In 10–12-kg pigs, also ventilated with air, the corresponding values found by Trouwborst were 36 $g \cdot l^{-1}$ (hematocrit $\approx$ 11%), 44%, and 0.57.[26] In the current study, similar low Sv_{O_2} values were obtained at $F_{I_{O_2}} = 0.35$ (table 2) but all animals survived longer than 1.5 h of ventilation at a lower $F_{I_{O_2}}$. Hemodilution increased myocardial blood flow, and reducing the $F_{I_{O_2}}$ from 1.0 to 0.15 caused a further increase (table 3). The severe hemodilution thus did not exhaust the potential for coronary vasodilation. All hemodiluted animals survived 30 min at $F_{I_{O_2}} = 0.10$ but at this stage oxygen uptake decreased, and arterial lactate and myocardial lactate production increased (figs. 1 and 2 and tables 2 and 3).

In conclusion, pigs hemodiluted to a hematocrit of 11% maintained a capacity for further increases in coronary blood flow, and survived a decrease in $F_{I_{O_2}}$ to 0.10. Increased systemic and myocardial lactate production occurred at similar systemic oxygen delivery rates in hemodiluted animals and in animals with normal hematocrit. Our data suggest that mixed venous oxygen saturation may be a less reliable indicator of inadequate oxygen delivery during hemodilution.

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