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Intestinal and Cerebral Oxygenation during Severe Isovolemic Hemodilution and Subsequent Hyperoxic Ventilation in a Pig Model

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Background: **During severe isovolemic hemodilution, determination of critical hematocrit levels for the microvascular oxygenation of different organs might provide more insight into the effect of the redistribution of blood flow and oxygen delivery on the oxygenation of different organs. The effect of an increased amount of dissolved oxygen on tissue oxygenation during severely decreased hematocrit levels is not clear.**

Methods: **Fifteen anesthetized pigs were randomized between an experimental group (n = 10), in which severe isovolemic hemodilution was performed with 6% hydroxyethylstarch (1:1), and a time-matched control group (n = 5). Systemic, intestinal, and cerebral hemodynamic and oxygenation parameters were monitored. Microvascular oxygen partial pressure (μPo_2) was measured in the cerebral cortex and the intestinal serosa and mucosa, using the oxygen-dependent quenching of Pd-porphyrin phosphorescence. In the final phase of the experiment, fraction of inspired oxygen was increased to 1.0.**

Results: **Hemodilution decreased hematocrit from 25.3 ± 3.0 to 7.6 ± 1.2% (mean ± SD). Systemic and intestinal oxygen delivery fell with the onset of hemodilution; intestinal oxygen consumption deceased at a hematocrit of 9.9%, whereas the systemic oxygen consumption decreased at a hematocrit of 7.6%. During hemodilution, the intestinal and cerebral oxygen extraction ratios increased from baseline with 130 and 52%, respectively. Based on the intersection of the two best-fit regression lines, determined by a least sum of squares technique, similar critical hematocrit levels were found for systemic oxygen consumption and the cerebral and intestinal mucosa μPo_2; the intestinal serosa μPo_2 decreased at an earlier stage ($P < 0.05$). Hyperoxic ventilation improved the μPo_2 values but not systemic or intestinal oxygen consumption.**

Conclusions: **During isovolemic hemodilution, the diminished oxygen supply was redistributed in favor of organs with a lower capacity to increase oxygen extraction. It is hypothesized that redirection of the oxygen supply within the intestines resulted in the preservation of oxygen consumption and mucosal μPo_2 compared with serosal μPo_2.**

ACUTE isovolemic hemodilution is a commonly used technique to delay or eliminate the need for transfusion of homologous blood during surgery. Although the oxygen content of the blood is reduced during this procedure, the whole body oxygen consumption ($\dot{V}o_2$) is maintained by an increase in cardiac output and an increase in the oxygen extraction ratio (O_2ER) of the tissues. A critical level of hemodilution is reached when the oxygen delivery (Do_2) falls below a critical point and compensatory mechanisms become insufficient: $\dot{V}o_2$ becomes dependent on supply, decreasing at the same rate as the Do_2. Such critical levels of hemodilution have been determined for systemic Do_2 and $\dot{V}o_2$ in anesthetized animals[1–5] and in an anesthetized human patient.[6] In a similar way, a critical level of hemodilution can be determined for an organ system: using an anesthetized rat model, similar critical levels of hemodilution were found for the intestinal oxygen consumption and intestinal microvascular oxygen partial pressure (μPo_2).[7]

During hemodilution, a redistribution of cardiac output and oxygen transport occurs in favor of organs with a lower capacity to increase oxygen extraction, *i.e.*, heart and brain.[8–11] Other organs, for example, the intestines, are supposed to compensate for the decreased oxygen content of the blood, mainly by an increase in oxygen extraction.[1,12,13] In a similar way, a redistribution of the oxygen flux might occur within an organ during hemodilution.[8,14] Thus, it can be hypothesized that a critical hemodilution level for the systemic $\dot{V}o_2$ will not reflect the critical levels of hemodilution for the oxygenation of different organ systems; (parts of) organs that respond differently to a decrease in hematocrit might display different critical levels of hemodilution. Because in Jehovah's Witness patients hyperoxia has been used during critical anemia, we also hypothesized that beyond these critical hemodilution levels, an increase in the arterial oxygen content caused by an increase in the inspired oxygen fraction (Fio_2) to 1.0 could restore local and systemic oxygenation.

Based on these hypotheses, the present study was designed to determine the critical levels of hemodilution for the oxygen consumption of the whole body and the intestines. In addition, critical levels were determined for the microvascular oxygenation of the cerebral cortex and the intestinal mucosa and serosa. Comparison of the latter two parameters with the intestinal oxygen consumption was expected to provide more insight into the redistribution of the oxygen flux within the intestines during isovolemic hemodilution. Because in a rat model, which was used in a previous study,[7] only the intestinal oxygenation could be assessed, an anesthetized pig

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model was used for the present study, with the additional advantage that the responses of this animal to several conditions of stress have been demonstrated to be similar to those of humans.[15,16]

Materials and Methods

Animals

The protocol of the present study was approved by the Animal Research Committee of the Academic Medical Center at the University of Amsterdam. Animal care and handling were performed in accordance with the national guidelines for care of laboratory animals. The experiments were performed in 15 crossbred Landrace x Yorkshire pigs, 10–12 weeks old, with a mean (± SD) body weight of 25 ± 2 kg.

Experimental Preparation

After an overnight fast with free access to water, the animals were sedated with an intramuscular injection of ketamine (20 mg/kg), midazolam (1 mg/kg), and atropine (0.5 mg). Anesthesia was induced with thiopental (5 mg/kg intravenously) and was maintained by intravenous infusion of midazolam (0.2 mg/kg bolus, followed by 0.2 mg · kg^{-1} · h^{-1}) and fentanyl (20 μg/kg bolus, followed by 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Muscle relaxation was obtained with pancuronium bromide (0.1 mg/kg bolus, followed by 0.1 mg · kg^{-1} · h^{-1}).

Identical anesthetic protocols have proven to be adequate for similar acute experiments in pigs.[8,14,17,18] One separate time-matched sham-operated animal was anesthetized without the use of muscle relaxants to ensure that the anesthetic regimen was adequate. After tracheal intubation, ventilation was performed (AV-1; Dräger-werke, Lübeck, Germany) with oxygen in air (F_{IO_2}, 0.33), maintaining normocapnia. As maintenance fluid, a crystalloid solution (Ringer's lactate) was administered (15 ml · kg^{-1} · h^{-1}). Central body temperature was maintained at approximately 37°C with a heating pad and isolation blankets.

Catheters were placed in the right brachial artery (6 French) for the measurement of arterial blood pressure and collection of arterial blood samples, the right brachial vein (14 gauge) for the administration of fluids, and the left femoral artery (8 French) for blood withdrawal during exchange transfusion. For the collection of jugular venous blood samples, a catheter (4 French) was inserted cranially into the right internal jugular vein in such a way that the tip of the catheter reached at least to the base of the skull. In this way, the internal jugular venous oxygen measurements were assumed to reflect the venous outflow of the brain in the jugular bulb, with a minimum of extracranial contamination.[19] A pulmonary artery thermodilution catheter (Edwards 7 French; Baxter Healthcare Corp., Round Lake, IL) was positioned in the pulmonary artery *via* an introducer in the left femoral vein for the measurement of cardiac output, right atrial pressure (RAP), pulmonary artery pressure, pulmonary capillary wedge pressure, central body temperature, and collection of mixed venous blood samples.

Following identification of the right carotid bifurcation, the external carotid artery was ligated immediately distal from the bifurcation, and an ultrasonic flow probe (3.0 mm; Transonic Systems Inc., Ithaca, NY) was placed around the right common carotid artery. If there was any artery branching from the internal carotid artery between the flow probe and the base of the skull (for instance, the occipital artery), this vessel was ligated as well.

Following midline laparotomy, an ultrasonic flow probe (4.0 mm; Transonic Systems Inc.) was placed around the superior mesenteric artery for the measurement of blood flow to the splanchnic region. After location of the terminal ileum, a mesenteric vein related to the ileum was cannulated (6 French) for the collection of mesenteric venous blood samples. An antimesenteric incision was made to expose the intestinal mucosa. The urinary bladder was cannulated to prevent distension of the bladder wall and to monitor urinary production.

A 5 × 5-cm skin flap was removed from the right side of the skull. A circular piece of bone (approximately 2 cm in diameter) was removed, exposing the dura mater of the brain. The dura was opened carefully until the cortical surface of the right hemisphere was clearly visible. Continuous irrigation with warmed saline prevented the exposed tissues from desiccation.

Hemodynamic and Blood Gas Measurements

Systolic and diastolic arterial blood pressures (millimeters of mercury), heart rate (beats per minute), RAP (millimeters of mercury), systolic and diastolic pulmonary pressures (millimeters of mercury), and pulmonary capillary wedge pressure (millimeters of mercury) were monitored. Cardiac output was measured by thermodilution and a cardiac output computer (Vigilance; Baxter Edwards Critical Care, Round Lake, IL). The average of 3 consecutive bolus injections of 5 ml of room-temperature saline was considered representative for the cardiac output at each measurement point. Blood flows in the internal carotid artery ($\dot{Q}_{ICA}$) and superior mesenteric artery ($\dot{Q}_{SMA}$) were measured continuously (Flow meter T206; Transonic Systems Inc.). By distal occlusion of the vessels, zero flow values were obtained, which were compared with the values measured at the end of the experiment after the animal had been killed. Hemodynamic values were indexed according to body weight. Systemic vascular resistance index, mesenteric vascular resistance index, and internal carotid vascular resistance index (all millimeters of mercury per milliliter per

Table 1. Hemodynamic Measurements during Isovolemic Hemodilution and Hyperoxia

		Baseline	20 ml	40 ml	60 ml	90 ml	Hyperoxia
Ht (%)	H	25.3 ± 3.0	17.0 ± 2.1*‡	12.8 ± 1.3*†‡	9.9 ± 1.1*†‡	7.6 ± 1.2*†‡	8.0 ± 1.4*‡
	C	25.7 ± 2.8	25.1 ± 2.8	25.1 ± 1.5	24.9 ± 1.2	27.2 ± 1.4	26.8 ± 2.3
HR (beats/min)	H	130 ± 13‡	140 ± 13‡	139 ± 12‡	152 ± 15*‡	159 ± 10*‡	141 ± 11†‡
	C	112 ± 14	116 ± 16	119 ± 12	115 ± 13	125 ± 9	110 ± 12
MAP (mmHg)	H	105 ± 7	108 ± 7	105 ± 9	96 ± 8	94 ± 9	97 ± 8
	C	101 ± 8	106 ± 8	107 ± 10	105 ± 8	103 ± 7	103 ± 8
MPAP (mmHg)	H	20 ± 3	21 ± 6	25 ± 4	24 ± 3	26 ± 6	25 ± 8
	C	19 ± 7	21 ± 5	23 ± 6	23 ± 7	22 ± 4	20 ± 4
PCWP (mmHg)	H	10 ± 3	11 ± 3	13 ± 3	12 ± 3	13 ± 3	15 ± 4*
	C	12 ± 2	11 ± 3	12 ± 3	12 ± 3	12 ± 3	14 ± 3
SVI (ml/kg)	H	1.8 ± 0.3	1.8 ± 0.3	2.0 ± 0.3	1.9 ± 0.3	1.9 ± 0.2	1.9 ± 0.2
	C	1.8 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	1.6 ± 0.3	1.5 ± 0.3	1.7 ± 0.3
SVRI ($mmHg \cdot l^{-1} \cdot kg^{-1} \cdot min^{-1}$)	H	35 ± 5	32 ± 5‡	28 ± 5*‡	24 ± 4*‡	20 ± 3*‡	24 ± 3*‡
	C	38 ± 5	41 ± 7	40 ± 7	42 ± 7	43 ± 8	44 ± 9
PVRI ($mmHg \cdot l^{-1} \cdot kg^{-1} \cdot min^{-1}$)	H	5 ± 2	4 ± 1	5 ± 2	4 ± 1	4 ± 2	4 ± 2
	C	4 ± 2	4 ± 2	4 ± 2	4 ± 2	5 ± 2	3 ± 2
MVRI ($mmHg \cdot l^{-1} \cdot kg^{-1} \cdot min^{-1}$)	H	226 ± 46‡	236 ± 52‡	213 ± 42‡	191 ± 45‡	167 ± 29*‡	190 ± 31‡
	C	290 ± 47	309 ± 35	324 ± 56	327 ± 52	324 ± 51	428 ± 35*
ICVRI ($mmHg \cdot l^{-1} \cdot kg^{-1} \cdot min^{-1}$)	H	3,182 ± 364	2,511 ± 384*	2,114 ± 374*†	1,763 ± 308*†‡	1,474 ± 350*†‡	2,017 ± 428*†‡
	C	2,694 ± 508	2,806 ± 494	2,798 ± 503	2,939 ± 497	2,826 ± 429	3,971 ± 563*

Values are presented as mean ± SD.

* $P < 0.05$ *versus* baseline 1 and 2. † $P < 0.05$ *versus* previous measurement. ‡ $P < 0.05$ *versus* control.

Ht = hematocrit; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure ; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; MVRI = mesenteric vascular resistance index; ICVRI = internal carotid vascular resistance index.

minute per kilogram) were calculated as follows: (MAP − RAP)/CI, (MAP − RAP)/$\dot{Q}_{SMA}$, and (MAP − RAP)/$\dot{Q}_{ICA}$, respectively, where MAP = mean arterial pressure.

At each measurement point, simultaneously an arterial sample was taken from the brachial artery, a mixed venous sample from the pulmonary artery catheter, a mesenteric venous sample from the mesenteric venous catheter, and a jugular venous sample from the internal jugular venous catheter. The samples were used to determine blood gas values (ABL505; Radiometer, Copenhagen, Denmark), as well as hematocrit, hemoglobin concentration, and hemoglobin oxygen saturation (So_2) (OSM 3; Radiometer), corrected for species.

Systemic Do2 (Do_{2SYS}; milliliters per minute per kilogram body weight) was calculated as:

$$CI \times \text{arterial } O_2 \text{ content},$$

where CI is expressed as milliliters per minute per kilogram, and arterial oxygen content is expressed as milliliters oxygen per milliliter blood, which was calculated as:

$$((1.31 \times [Hb] \times Sa_{O_2}) + (0.003 \times Pa_{O_2})) \times 0.01,$$

where Pa_{O_2} is arterial oxygen partial pressure and Sa_{O_2} is arterial oxygen saturation. Systemic oxygen consumption ($\dot{V}o_{2SYS}$; milliliters per minute per kilogram bodyweight) was calculated as:

$$CI \times (\text{arterial} - \text{mixed venous } O_2 \text{ content difference}).$$

The systemic O_2ER (O_2ER_{SYS}; percent) was calculated as:

$$(\text{arterio} - \text{mixed venous } O_2 \text{ content difference})/\text{arterial } O_2 \text{ content}.$$

In a similar way, the intestinal Do_2 (DO_{2SMA}), $\dot{V}o_2$ ($\dot{V}o_{2SMA}$), and O_2ER (O_2ER_{SMA}) were calculated. Measurement of the internal jugular venous oxygen content allowed the calculation of the arteriovenous oxygen content difference, and thereby the O_2ER of the brain[20–22] (O_2ER_{ICA}) was calculated as:

$$(\text{arterio} - \text{internal jugular venous } O_2 \text{ content difference})/\text{arterial } O_2 \text{ content}.$$

Microvascular Oxygen Partial Pressure Measurements

The μPo_2 was measured in the cerebral cortex and the serosa and mucosa of the ileum, using the oxygen-dependent quenching of Pd-porphyrin phosphorescence. Excitation of Pd-porphyrin by a pulse of light causes emission of phosphorescence with a decay in time, which is quantitatively related to the oxygen concentration.[23–25] Pd-meso-tetra(4 carboxy-phenyl)porphine (Porphyrin Products, Logan, UT) is coupled to human serum albumin to form a large molecular complex that, when injected intravenously, is confined mainly to the vascular compartment.[25,26] Fifty milliliters of a 4-mM Pd-porphyrin solution was administered, corresponding with a dosage of 12 mg/kg bodyweight. The μPo_2 measurements were made with optical fibers for the trans-

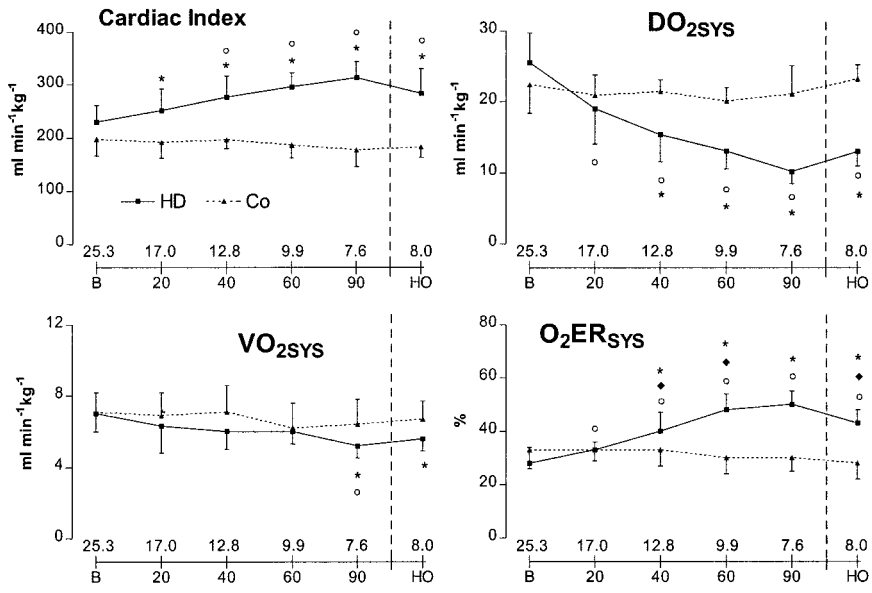


Fig. 1. Systemic blood flow and oxygenation parameters after 20, 40, 60, and 90 ml/kg hemodilution (with hematocrit values) and consequent hyperoxic ventilation (HO, beyond dotted line) in 10 anesthetized pigs (HD) and at corresponding time points in 5 control animals (Co). Cardiac index (CI) increased during hemodilution. Systemic oxygen delivery (Do_{2SYS}) decreased with the onset of hemodilution, whereas the systemic oxygen consumption ($\dot{V}o_{2SYS}$) decreased after the final hemodilution step. Systemic oxygen extraction ratio (O_2ER_{SYS}) increased significantly. Hyperoxia had no significant effect on these parameters. Values represent mean ± SD. *P < 0.05 HD *versus* Co; ○P < 0.05 HD *versus* baseline; ◆P < 0.05 HD *versus* previous.

mission of excitation and emission light, attached to a phosphorimeter. To determine which microvascular compartment is measured by fiber phosphorimetry, the Pd-porphyrin phosphorescence fiber technique has been compared with a microscopic phosphorimeter: simultaneous Po_2 measurements with the fiberoptic technique showed excellent correlation with microscopically measured Po_2 in capillaries and first-order venules, but not with arteriolar or venous Po_2 values, at different Fio_2 levels.[27] Thus, this result allowed us to term the fiberoptic measurement of Po_2 as the measurement of μPo_2. Fiberoptic measurements of μPo_2 incorporate blood vessels over an area of approximately 1 cm^2 with a penetration depth of approximately 0.5 mm.[17,25] As the calibration constants in the calculation of the μPo_2 from the phosphorescence decay time are temperature dependent, intestinal surface temperature measurements were used for correction of these constants. In the present study, a multifiber phosphorimeter was used, with three separately operated optical fibers. The fibers were placed near the surfaces of the cerebral cortex and the serosa and mucosa of the ileum. In this way, the μPo_2 was measured in three different regions simultaneously.

Experimental Procedure

After preparation and a stabilization period of at least 30 min, two baseline measurements were made during a 1-h period. The animals were randomized between a hemodilution group (n = 10) and a time-matched control group (n = 5). Stepwise isovolemic hemodilution was accomplished by withdrawal of blood from the femoral artery and simultaneous administration of an equal volume of HAES-steril 6% (6% hydroxyethylstarch, degree of substitution 0.5, in 0.9% NaCl solution, Mw 200,000; Fresenius, Germany) through the femoral vein at the same rate. Four dilution steps were made: three steps of 20 ml/kg bodyweight and a final step of 30 ml/kg, resulting in a total volume exchange of 90 ml/kg. Twenty minutes after each hemodilution step, all hemodynamic, blood gas, and μPo_2 measurements were repeated. Lactate measurements were performed at baseline and after a total volume exchange of 40 and 90 ml/kg. Following the measurements after the final hemodilution step, Fio_2 was increased to 1.0, and after 20 min stabilization, all measurements were repeated. In the control group, identical measurements were made at corresponding time intervals, but no hemodilution was performed. In the final stage of the experiment, the Fio_2 was increased to 1.0. All experiments were terminated by administration of 30 mmol of potassium chloride.

Statistical Analysis

Values are reported as mean ± SD. Because the consecutive baseline measurements were not significantly different for any parameter, they were averaged and presented as a single data point. Intragroup differences were analyzed using analysis of variance for repeated measurements. When appropriate, *post hoc* analyses were performed with the Student-Newman-Keuls test. Intergroup differences for each measurement point were analyzed with the unpaired *t* test; Bonferroni correction for multiple comparisons was used. *P* values < 0.05 were considered significant. A critical level of hemodilution was determined for the whole body $\dot{V}o_2$ and the μPo_2 of the intestinal serosa and mucosa and the cerebral cortex. From plots of hematocrit against $\dot{V}o_{2SYS}$ and μPo_2, it was possible to determine the points at which $\dot{V}o_2$ or μPo_2 became dependent on the hematocrit with further hemodilution. These points were determined for each animal separately by the intersection of

Table 2. Systemic Blood Gas and Lactate Measurements during Isovolemic Hemodilution and Hyperoxia

		Baseline	20 ml	40 ml	60 ml	90 ml	Hyperoxia
Ht (%)	H	25.3 ± 3.0	17.0 ± 2.1*†‡	12.8 ± .3*†‡	9.9 ± 1.1*†‡	7.6 ± 1.2*†‡	8.0 ± 1.4*‡
	C	25.7 ± 2.8	25.1 ± 2.8	25.1 ± 1.5	24.9 ± 1.2	27.2 ± 1.4	26.8 ± 2.3
Hb (g/dl)	H	8.1 ± 1.0	5.4 ± 0.7*	3.9 ± 0.7*†	3.0 ± 0.4*†	2.2 ± 0.2*†	2.4 ± 0.5*
	C	8.3 ± 0.9	8.1 ± 0.9	8.1 ± 0.5	8.0 ± 0.4	8.8 ± 0.6	8.6 ± 0.8
Sa_{O_2} (%)	H	99.5 ± 0.5	99.5 ± 0.5	99.2 ± 0.4	99.7 ± 0.5	99.4 ± 0.5	99.9 ± 0.3
	C	99.4 ± 1.0	99.6 ± 0.5	99.0 ± 0.7	99.0 ± 0.2	99.0 ± 0.7	100 ± 0.0
Pa_{O_2} (mm Hg)	H	166 ± 14	175 ± 10	169 ± 18	172 ± 12	162 ± 16	499 ± 44*†‡
	C	173 ± 9	180 ± 8	177 ± 9	174 ± 8	171 ± 10	568 ± 25*†
Ca_{O_2} (ml/dl)	H	11.0 ± 1.4	7.5 ± 0.9*‡	5.5 ± 0.7*†‡	4.4 ± 0.7*†‡	3.4 ± 0.3*†‡	4.7 ± 0.5*†‡
	C	10.9 ± 1.1	11.1 ± 1.2	11.0 ± 0.6	10.9 ± 0.4	11.9 ± 0.6	13.0 ± 0.9*†
Pa_{CO_2} (mmHg)	H	37 ± 3	36 ± 4	38 ± 2	37 ± 3	39 ± 3	41 ± 5
	C	37 ± 2	38 ± 5	39 ± 2	37 ± 3	40 ± 3	36 ± 2
pHa	H	7.48 ± 0.03	7.49 ± 0.03	7.47 ± 0.03	7.46 ± 0.03	7.44 ± 0.03*	7.43 ± 0.06*
	C	7.49 ± 0.03	7.48 ± 0.03	7.48 ± 0.03	7.48 ± 0.05	7.45 ± 0.04	7.51 ± 0.04†
Lac art (mM)	H	1.38 ± 0.21	—	1.30 ± 0.18‡	—	1.66 ± 0.31	1.58 ± 0.29
	C	1.54 ± 0.25	—	1.63 ± 0.21	—	1.31 ± 0.29	1.40 ± 0.31
$S\bar{v}_{O_2}$ (%)	H	73 ± 6	69 ± 8	63 ± 8*†	54 ± 9*†‡	52 ± 9*‡	80 ± 7*†
	C	69 ± 7	69 ± 4	68 ± 6	71 ± 6	71 ± 5	81 ± 6*†
$P\bar{v}_{O_2}$ (mmHg)	H	48 ± 5	44 ± 3	40 ± 4*†‡	37 ± 3*‡	37 ± 3*‡	54 ± 6*†
	C	44 ± 4	45 ± 3	45 ± 4	46 ± 4	46 ± 4	55 ± 8
$pH\bar{v}$	H	7.44 ± 0.04	7.43 ± 0.03	7.42 ± 0.04	7.40 ± 0.04	7.38 ± 0.03	7.36 ± 0.06*‡
	C	7.45 ± 0.03	7.44 ± 0.03	7.44 ± 0.03	7.43 ± 0.04	7.42 ± 0.04	7.46 ± 0.05
Lac mix (mM)	H	1.37 ± 0.28	—	1.44 ± 0.27	—	1.80 ± 0.36	1.57 ± 0.37
	C	1.60 ± 0.21	—	1.65 ± 0.29	—	1.47 ± 0.16	1.39 ± 0.22

Values are presented as mean ± SD.

* $P < 0.05$ *versus* baseline 1 and 2. † $P < 0.05$ *versus* previous measurement. ‡ $P < 0.05$ *versus* control.

Ht = hematocrit; Hb = hemoglobin; Sa_{O_2} = arterial o_2 saturation; Pa_{O_2}; arterial tension o_2; Ca_{O_2} = arterial o_2 content; Pa_{CO_2} = arterial partial pressure of co_2; pHa = arterial pH; Lac art = arterial lactate concentration; $S\bar{v}_{O_2}$ = mixed venous O_2 saturation; $P\bar{v}_{O_2}$ = mixed venous partial pressure of O_2; $pH\bar{v}$ = mixed venous pH; Lac mix = mixed venous lactate concentration.

the two best-fit regression lines, as determined by a least sum of squares technique.

Results

Systemic and Pulmonary Hemodynamics

Because of the type of measurements, muscle relaxation was necessary throughout the experimental protocol. To ensure that the anesthetic regimen was sound, one separate time-matched sham-operated animal was anesthetized without the use of muscle relaxants. Throughout the experiment, the animal did not try to escape or move purposefully. Only slight shivering was observed 150 min after start of anesthesia. All hemodynamic parameters remained stable as in all control group animals. All hemodynamics of the study animals are summarized in table 1.

Baseline measurements in the hemodilution and the control groups were not significantly different, except for the heart rate, which was lower in the control group. In the control animals, all systemic hemodynamic parameters remained constant throughout the experiment. In the hemodilution group, the decrease in hematocrit, from 25.3 ± 3.0 at baseline to 7.6 ± 1.2% after exchange of 90 ml/kg, was accompanied by an increase in cardiac index (CI; fig. 1). Heart rate increased significantly, whereas stroke volume did not change from baseline values. MAP remained constant during hemodilution, although the systemic vascular resistance index decreased significantly compared with baseline and control group values. The pulmonary artery pressure, vascular resistance index, and pulmonary capillary wedge pressure did not change significantly during hemodilution.

Hyperoxia decreased the heart rate to the range of baseline values, resulting in a slight but not significant decrease in CI. In addition, the pulmonary capillary wedge pressure and the systemic vascular resistance index increased after hyperoxia.

Systemic Oxygenation

Data are summarized in table 2 and figure 1. Despite the increase in CI, Do_{2SYS} decreased with the onset of hemodilution. The O_2ER_{SYS} increased, and as a result the $\dot{V}o_{2SYS}$ was preserved through a hematocrit of 9.9% but decreased significantly after the final hemodilution step at a hematocrit of 7.6%. Consequently, the mixed venous Po_2 and So_2 decreased with progressive hemodilution.

Following the final dilution step, hyperoxia significantly increased the arterial oxygen content in the hemodilution group from 3.4 ± 0.3 to 4.7 ± 0.5 ml/dl. This did not change Do_{2SYS}, despite the decrease in CI. The O_2ER_{SYS} decreased significantly following hyperoxia, and $\dot{V}o_{2SYS}$ was not restored. Mixed venous Po_2 and So_2 increased above baseline values ($P < 0.05$). In the control group, the arterial oxygen content was increased by hyperoxia as well. However, this did not change the

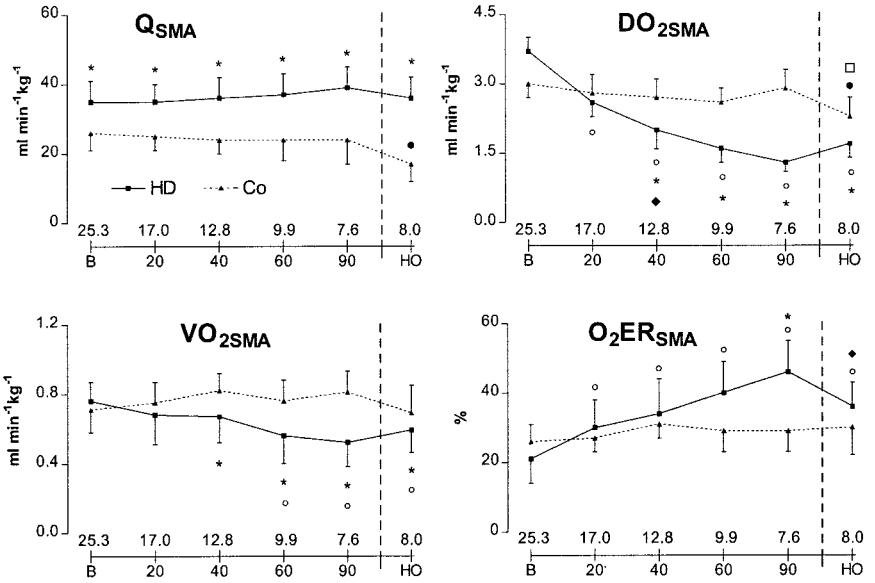


Fig. 2. Intestinal blood flow and oxygenation parameters after 20, 40, 60, and 90 ml/kg hemodilution (with hematocrit values) and consequent hyperoxic ventilation (HO, beyond dotted line) in 10 anesthetized pigs (HD) and at corresponding time points in 5 control animals (Co). Superior mesenteric artery blood flow ($\dot{Q}_{SMA}$) did not change during hemodilution. Superior mesenteric artery oxygen delivery (Do_{2SMA}) decreased with the onset of hemodilution; $\dot{V}o_{2SMA}$ decreased after the third hemodilution step. Superior mesenteric artery oxygen extraction ratio (O_2ER_{SMA}) increased progressively during the experiment. Hyperoxia significantly decreased $\dot{Q}_{SMA}$ and Do_{2SMA} in the control group and O_2ER_{SMA} in the hemodilution group. Values represent mean ± SD. *P < 0.05 HD *versus* Co; ○P < 0.05 HD *versus* baseline; ◆P < 0.05 HD *versus* previous.

Do_{2SYS} and $\dot{V}o_{2SYS}$, although mixed venous Po_2 and So_2 exceeded baseline values.

Regional Blood Flow and Oxygenation

Although all animals underwent the same surgical and anesthetic protocols and were randomly assigned to the hemodilution or the control group, mesenteric blood flow ($\dot{Q}_{SMA}$) in the control group was lower (fig. 2) compared with the hemodilution group. All control group parameters remained constant. Hemodilution did not change $\dot{Q}_{SMA}$, resulting in a progressive decrease in Do_{2SMA}. After exchange of 60 ml/kg (corresponding hematocrit, 9.9%), $\dot{V}o_{2SMA}$ was decreased from baseline, whereas O_2ER_{SMA} increased from 21 ± 7% at baseline to 46 ± 9% after the final hemodilution step (fig. 2).

Baseline values for the carotid blood flow ($\dot{Q}_{ICA}$; fig. 3) and the corresponding vascular resistance (table 1) were comparable for both groups. $\dot{Q}_{ICA}$ increased from 2.5 ± 0.5 ml · min^{-1} · kg^{-1} at baseline to 4.2 ± 0.6 ml · min^{-1} · kg^{-1} after exchange of 90 ml/kg (fig. 3). Internal jugular venous Po_2 (fig. 4) and So_2 (table 3) decreased during hemodilution, reflecting the increase in O_2ER_{ICA} (from 30 ± 6% at baseline to 47 ± 6% at 90-ml/kg exchange; fig. 3). Mesenteric venous Po_2 (fig. 4) and So_2 values (table 3) decreased in a similar way.

Hyperoxia did not influence $\dot{Q}_{SMA}$ after hemodilution. The Do_{2SMA} increased slightly but not significantly, and $\dot{V}o_{2SMA}$ did not improve. Mesenteric venous Po_2 and So_2 increased substantially following hyperoxia; the Po_2 even exceeded baseline values. In the control group, however, the mesenteric vascular resistance index increased after hyperoxia and the $\dot{Q}_{SMA}$ decreased, resulting in a decrease in Do_{2SMA} but not in $\dot{V}o_{2SMA}$. The change in O_2ER_{SMA} was not statistically significant, and the mesenteric venous Po_2 and So_2 did not significantly increase after hyperoxia in the control group.

Hyperoxia decreased the $\dot{Q}_{ICA}$ significantly in the hemodilution and the control groups. Po_2 and So_2 in the internal jugular vein in the hemodilution group exceeded baseline values, whereas they did not change in the control group.

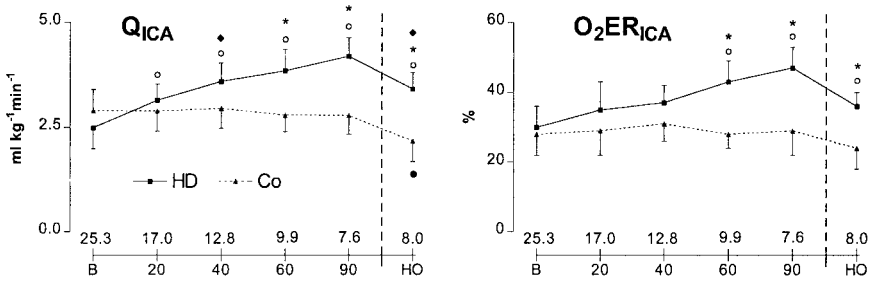


Fig. 3. Internal carotid artery blood flow ($\dot{Q}_{ICA}$) and cerebral oxygen extraction ratio (O_2ER_{ICA}) after 20, 40, 60, and 90 ml/kg hemodilution (with hematocrit values) and consequent hyperoxic ventilation (HO, beyond dotted line) in 10 anesthetized pigs (HD) and at corresponding time points in 5 control animals (Co). $\dot{Q}_{ICA}$ increased after the first hemodilution step, O_2ER_{ICA} after the third hemodilution step. Hyperoxia had no significant effect on these parameters. Values represent mean ± SD. *P < 0.05 HD *versus* Co; ○P < 0.05 HD *versus* baseline; ◆P < 0.05 HD *versus* previous.

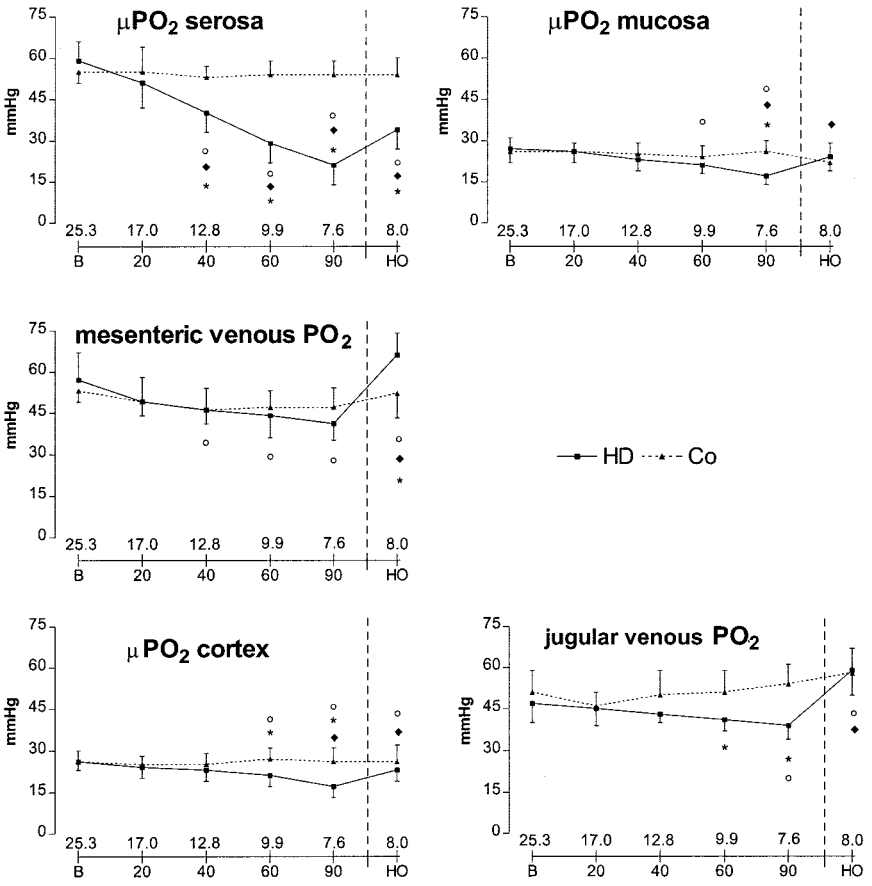


Fig. 4. Intestinal serosal and mucosal, and cerebral cortex microvascular oxygen partial pressure (μPo_2) and mesenteric and jugular venous Po_2 values after 20, 40, 60, and 90 ml/kg hemodilution (with hematocrit values) and consequent hyperoxic ventilation (HO, beyond dotted line) in 10 anesthetized pigs (HD) and at corresponding time points in 5 control animals (Co). Serosal μPo_2 decreased significantly after the second hemodilution step, whereas the mucosal μPo_2 fell after 60 ml/kg blood exchange. Mesenteric venous Po_2 decreased throughout the complete hemodilution procedure. Cerebral μPo_2 decreased significantly after the third hemodilution step, similar to the internal jugular venous Po_2. Hyperoxia increased all μPo_2 values and raised the venous Po_2 above baseline levels in the hemodilution group but had no significant effect on these parameters in the control group. Values represent mean ± SD. *$P < 0.05$ HD *versus* Co; ○$P < 0.05$ HD *versus* baseline; ◆$P < 0.05$ HD *versus* previous.

Microvascular Oxygen Partial Pressure Measurements

Microvascular and regional venous Po_2 measurements are shown in figure 4. Baseline measurements were similar for the hemodilution and the control groups. The μPo_2 of the serosa (59 ± 7 mmHg at baseline) decreased at the second hemodilution step and fell to 21 ± 7 mmHg after the last step (hematocrit, 7.6 ± 1.2%). The mucosal μPo_2 (27 ± 4 mmHg at baseline) remained unaffected for a longer period of time and was decreased after the third hemodilution step (hematocrit, 9.9 ± 1.1%). The μPo_2 of the cerebral cortex (26 ± 3 mmHg at baseline) demonstrated a similar behavior as the mucosal μPo_2 and was also decreased after the third hemodilution step. μPo_2 measurements in the control groups did not change in time.

Table 3. Regional Venous Blood Gas and Lactate Measurements during Hemodilution and Hyperoxia

		Baseline 1	20 ml	40 ml	60 ml	90 ml	Hyperoxia
Ht (%)	H	25.3 ± 3.0	17.0 ± 2.1*‡	12.8 ± 1.3*†‡	9.9 ± 1.1*†‡	7.6 ± 1.2*†‡	8.0 ± 1.4*‡
	C	25.7 ± 2.8	25.1 ± 2.8	25.1 ± 1.5	24.9 ± 1.2	27.2 ± 1.4	26.8 ± 2.3
$Smvo_2$ (%)	H	80 ± 8	74 ± 9	69 ± 9*	64 ± 10*	58 ± 9*	84 ± 9†
	C	76 ± 6	73 ± 6	70 ± 4	72 ± 5	72 ± 6	78 ± 8
pHmv	H	7.45 ± 0.03	7.43 ± 0.03	7.40 ± 0.03*†‡	7.39 ± 0.03*	7.35 ± 0.04*‡	7.35 ± 0.04*‡
	C	7.45 ± 0.03	7.43 ± 0.01	7.42 ± 0.01	7.42 ± 0.02	7.41 ± 0.02	7.43 ± 0.02
Lac mes (mM)	H	1.80 ± 0.25	—	1.55 ± 0.41	—	1.50 ± 0.47	1.46 ± 0.46
	C	1.72 ± 0.36	—	1.67 ± 0.38	—	1.51 ± 0.32	1.50 ± 0.31
$Sjvo_2$ (%)	H	70 ± 10	66 ± 8	66 ± 6	61 ± 8	57 ± 8*	83 ± 9*†
	C	73 ± 6	68 ± 4	70 ± 5	70 ± 6	73 ± 9	80 ± 5
pHjv	H	7.42 ± 0.04	7.42 ± 0.03	7.40 ± 0.02	7.37 ± 0.03*	7.35 ± 0.04*	7.34 ± 0.05*
	C	7.44 ± 0.04	7.42 ± 0.02	7.43 ± 0.01	7.42 ± 0.02	7.41 ± 0.02	7.44 ± 0.02
Lac jug (mM)	H	2.19 ± 0.43	—	2.15 ± 0.41	—	2.39 ± 0.46	2.40 ± 0.46
	C	2.16 ± 0.41	—	2.44 ± 0.48	—	2.03 ± 0.49	1.88 ± 0.39

Values are presented as mean ± SD.

* $P < 0.05$ *versus* baseline 1 and 2. † $P < 0.05$ *versus* previous measurement. ‡ $P < 0.05$ *versus* control.

Ht = hematocrit; $Smvo_2$ = mesenteric venous O_2 saturation; pHmv = mesenteric venous pH; Lac mes = mesenteric venous lactate concentration; $Sjvo_2$ = jugular venous O_2 saturation; pHjv = jugular venous pH; Lac jug = jugular venous lactate concentration.

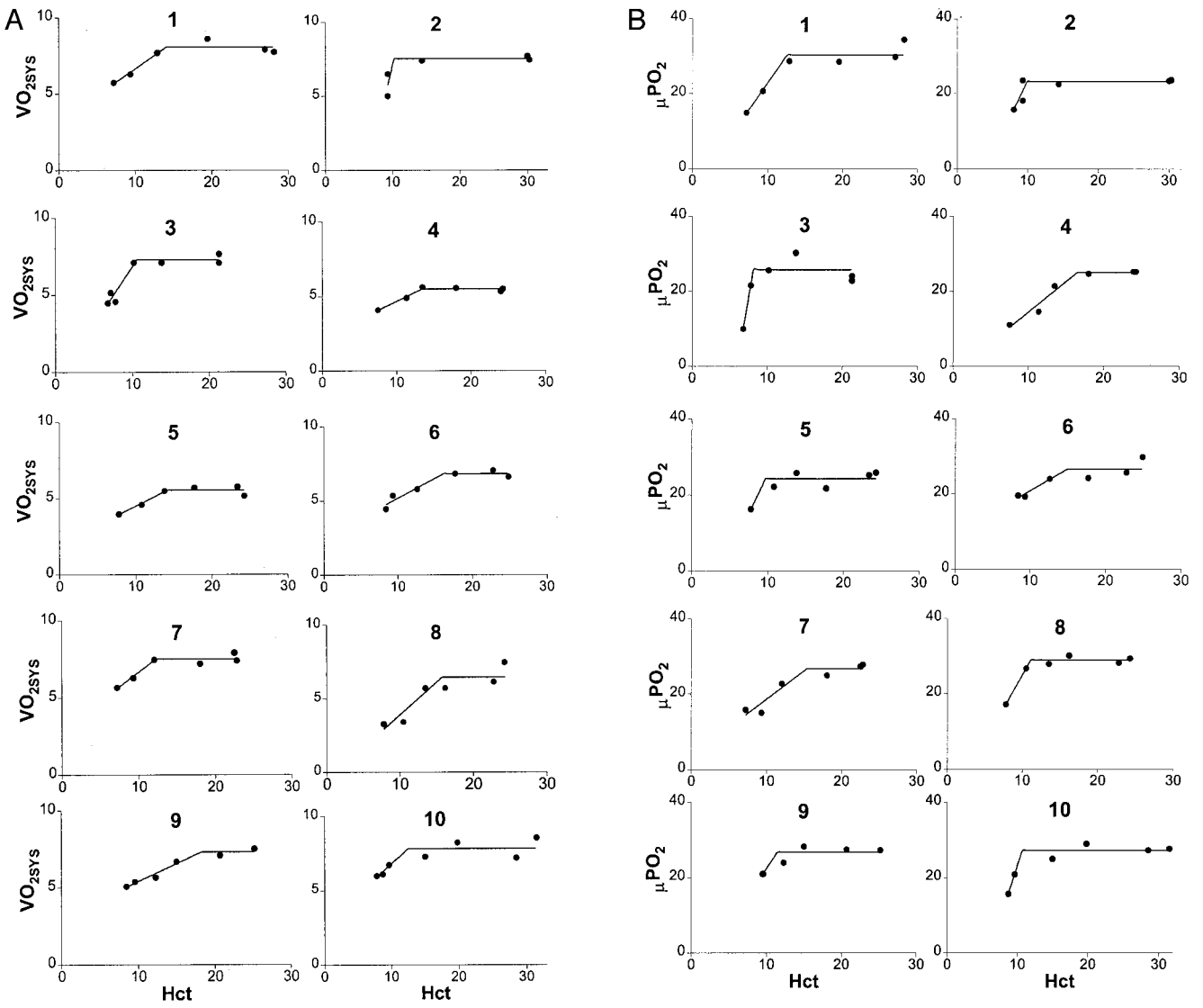
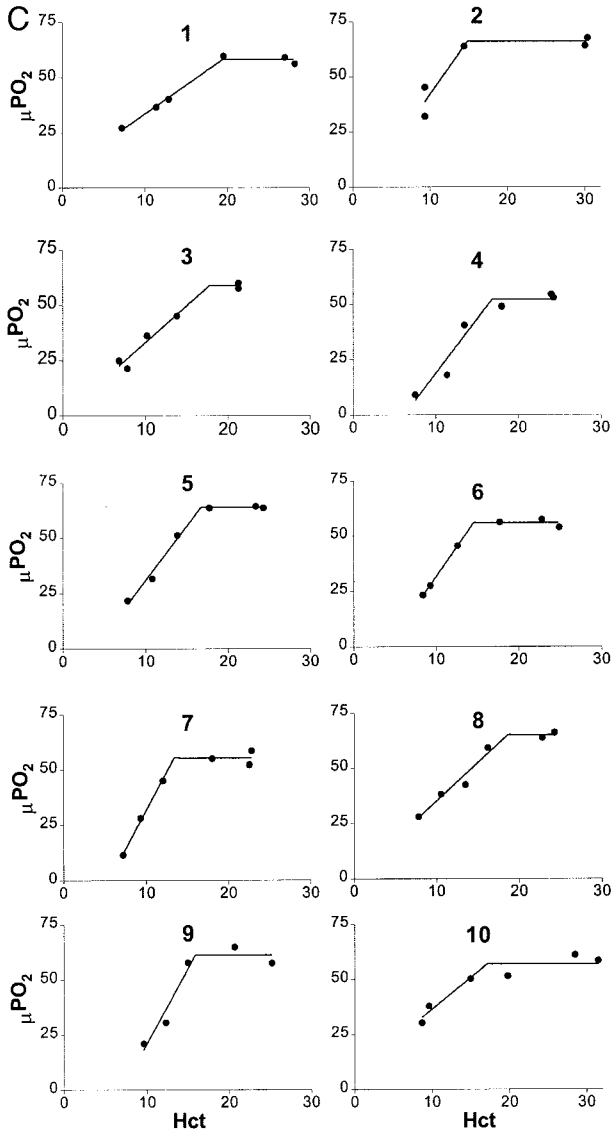


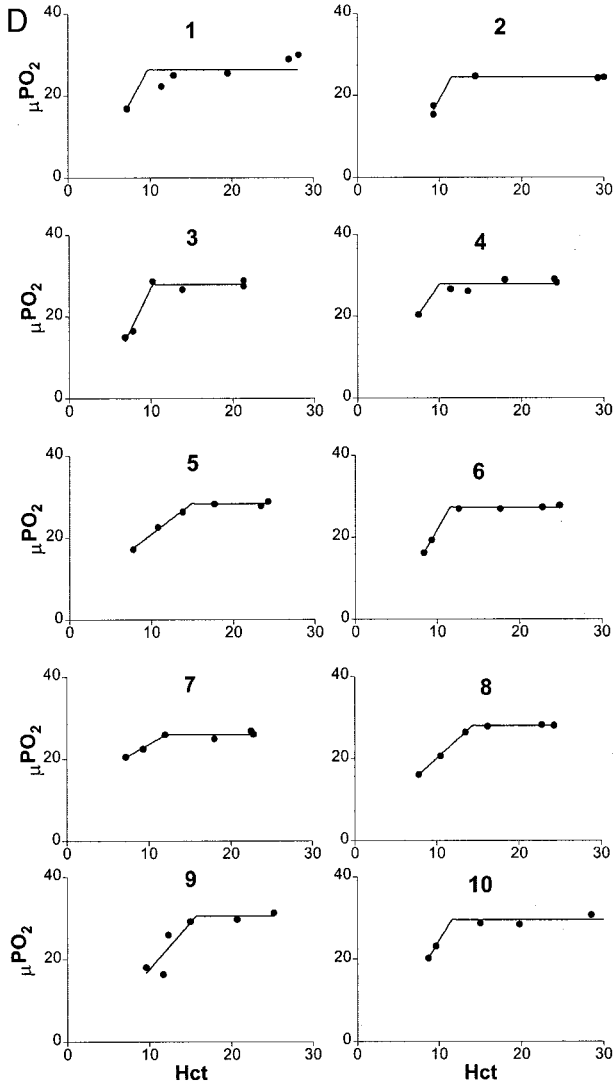
Fig. 5. (*A*) Critical levels of hemodilution for the systemic oxygen consumption ($\dot{V}O_2$), calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 13.7 ± 3.5%. (*B*) Critical levels of hemodilution for the mucosal microvascular oxygen partial pressure (μPO_2), calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 11.4 ± 2.6%. (*C*) Critical levels of hemodilution for the serosal μPO_2, calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 16.9 ± 4.2%, which was significantly higher than the critical hematocrit values of the mucosal and cerebral μPO_2 and systemic $\dot{V}O_2$. (*D*) Critical levels of hemodilution for the cerebral cortex μPO_2, calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 12.1 ± 3.1%.

In the hemodilution group, hyperoxia increased both the serosal and the mucosal μPO_2; the mucosal μPO_2 was even restored to baseline values. The cerebral cortex μPO_2 was also significantly increased but did not return to baseline values. Hyperoxia had no significant effect in the control group.

Critical Levels of Hemodilution

The critical hematocrit levels for the systemic $\dot{V}O_2$ and intestinal and cerebral μPO_2 measurements are shown in figure 5. $\dot{V}O_{2SYS}$ (fig. 5A) started to decrease with hemodilution at an average hematocrit of 13.7 ± 3.5%. In the intestines, the critical hematocrit for the intestinal mucosa (fig. 5B) was 11.4 ± 2.6%, whereas the serosal μPO_2 (fig. 5C) started to decrease with hematocrit already at an average value of 16.9 ± 4.2. The μPO_2 in the cerebral cortex (fig. 5D) displayed a similar behavior as the intestinal mucosa and $\dot{V}O_{2SYS}$ and started to decrease with hematocrit at an average value of 12.1 ± 3.1%. The critical hematocrit values for the mucosal and cerebral μPO_2 and $\dot{V}O_{2SYS}$ were not significantly different; compared with the serosal μPO_2, the critical hematocrit of the latter was found to be significantly higher.





Metabolic Parameters

Systemic and regional parameters are summarized in tables 2 and 3, respectively. Arterial carbon dioxide partial pressure did not change during the entire experiment in the hemodilution and the control groups. The systemic and regional venous *p*H measurements did not change in the control group. In the hemodilution group, the arterial *p*H decreased significantly after the final hemodilution step. The mixed venous *p*H did not change, but the mesenteric venous *p*H decreased after the second step and the jugular venous *p*H after the third step. There was no significant change in systemic and regional lactate levels during hemodilution.

Discussion

The main finding of this study is that the systemic $\dot{V}O_2$, the cerebral μPO_2, and the intestinal mucosal μPO_2 became impaired at the same stage during hemodilution, whereas the intestinal serosal μPO_2 became impaired at an earlier stage. The systemic response to the decreased arterial oxygen content consisted of an increase in CI and an increase in O_2ER_{SYS}. At a regional level, the increased CI was redistributed in favor of other organ systems than the intestines, as $\dot{Q}_{SMA}$ remained constant. Despite the redistribution of blood flow, systemic as well as intestinal $\dot{V}O_2$ became impaired by the diminished oxygen supply at the same level of hemodilution. Although systemic redistribution may have favored the oxygenation of, for instance, the brain, the intestines successfully compensated for the diminished DO_2 by a larger increase in the oxygen extraction from the blood: 130% increase for the intestinal *versus* 52% for the cerebral O_2ER from baseline to the final hemodilution step. An increase in O_2ER as the predominant mechanism for the preservation of intestinal $\dot{V}O_2$ has been reported in previous studies as well.[1,12,28] Finally, a level of hemodilution was reached below which all compensatory

mechanisms became insufficient, resulting in a general critical level of hemodilution for the whole body, the intestinal mucosa, and the cerebral cortex.

Redistribution of a diminished oxygen supply in favor of organ systems with a lower oxygen extraction capacity can increase the efficiency of D_{O_2}.[29] However, the mechanisms behind the redistribution of blood flow during hemodilution are not clear. The results of the present study demonstrated the functional consequences of redistribution and only allow for speculations to be made regarding regulatory mechanisms. Possible mechanisms that could account for systemic or local redistribution could include increased sympathetic activity,[30–32] although the level of circulating catecholamines does not increase during hemodilution.[8] On the other hand, activity of nitric oxide might play an important role in the systemic and splanchnic response to hemodilution.[33–35] An increase in cerebral blood flow during hemodilution has been attributed to decreases in arterial oxygen concentration and blood viscosity[36–38]; increased nitric oxide activity should not be involved in this process.[39]

Although the $\dot{V}_{O_{2SMA}}$ and the mucosal μP_{O_2} were preserved until a hematocrit of ±11.0%, the serosal μP_{O_2} started to decline at a hematocrit of 17.0% ($P < 0.05$). This finding implies that the mucosa contains the predominant oxygen-consuming part of the intestinal wall and is in agreement with the oxygen electrode measurements of Haisjackl *et al.*[14] during hemodilution. Being the site for absorption and secretion in the gastrointestinal tract and the barrier to microbial invasion from the intestinal lumen, the gut mucosa can be expected to have a greater oxygen demand than the serosa. To preserve these important functions during conditions of diminished oxygen supply, it is not unlikely that during hemodilution the diminished intestinal oxygen supply was redistributed in favor of the mucosa.[14,35] A redistribution of intraorgan blood flow during hemodilution has been shown to occur in the heart[8,40,41] and the kidney.[8]

In the present study, systemic and regional oxygenation became impaired in the hematocrit range of 10–15%, which is in agreement with critical values in previous studies.[2,4,6] In addition, the constant regional and systemic lactate concentrations in the present study point at adequate tissue oxygenation until this level of hemodilution,[42] to which is contributed by the values of the regional intestinal carbon dioxide partial pressure. At the lowest hematocrit levels, only the decreased *p*H values indicated that tissue oxygenation was impaired, although systemic or regional acidosis did not occur. Considering critical levels of hemodilution in general, it must be noted that anesthetized animals respond differently to hemodilution as compared with conscious animals. Although not supported by the results of the present study, in anesthetized animals cardiac output increased mainly because of an increase in stroke volume, whereas in conscious animals the increased cardiac output was attributable to an increment in heart rate.[43] The influence of anesthesia is emphasized by studies in which a critical level of D_{O_2} could not be demonstrated during hemodilution in conscious animals and humans.[44–46]

The increase in F_{IO_2} did not improve systemic or intestinal $\dot{V}_{O_2}$ despite an increase in arterial oxygen content in the hemodilution and the control groups. Furthermore, it was found that only at low hematocrit levels did hyperoxia increase the regional venous P_{O_2} values far more than the μP_{O_2} values, indicating that in combination with severe hemodilution, the increased amount of physically dissolved oxygen was being shunted to the venous side of the organ vascular beds. It can be hypothesized that an interaction between the physiologic responses to hemodilution (*e.g.*, increased capillary density and blood flow) on the one hand and hyperoxia (reduced capillary density and blood flow[47]) on the other hand resulted in at least a partial diversion of the dissolved oxygen away from the microcirculation.

In conclusion, similar critical levels of hemodilution were found for $\dot{V}_{O_{2SYS}}$ and the cerebral and intestinal mucosal μP_{O_2}, whereas the intestinal O_2ER increased to a greater extent than the cerebral O_2ER, indicating that during hemodilution the diminished oxygen supply was efficiently redistributed in favor of the organs with a lower capacity to increase oxygen extraction. The serosal μP_{O_2} decreased at an earlier stage than the mucosal μP_{O_2}, suggesting that the decreased intestinal oxygen supply was redistributed within the intestinal wall during hemodilution. During oxygen supply dependency, hyperoxic ventilation did not improve systemic or regional $\dot{V}_{O_2}$. The increased regional venous P_{O_2} values in combination with the decreased O_2ER indicate that the increased amount of physically dissolved oxygen was shunted to the venous side of the organ vascular beds during severe hemodilution.

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