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

Jasper van Bommel, M.D., Ph.D.,* Adrianus Trouwborst, M.D., Ph.D.,† Lothar Schwarte, M.D.,‡ Martin Siegemund, M.D.§ Can Ince, Ph.D.,|| Ch. Pieter Henny, M.D., Ph.D.#

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 (μPO2) 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 μPO2; the intestinal serosa μPO2 decreased at an earlier stage (P < 0.05). Hyperoxic ventilation improved the μPO2 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 μPO2 compared with serosal μPO2.

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 (VO2) is maintained by an increase in cardiac output and an increase in the oxygen extraction ratio (O2ER) of the tissues. A critical level of hemodilution is reached when the oxygen delivery (DO2) falls below a critical point and compensatory mechanisms become insufficient: VO2 becomes dependent on supply, decreasing at the same rate as the DO2. Such critical levels of hemodilution have been determined for systemic DO2 and VO2 in anesthetized animals1-5 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 (μPO2).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 VO2 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 (FiO2) 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...
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 μg·kg⁻¹·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; Drägerwerke, Lübeck, Germany) with oxygen in air (FIO₂, 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 splanchic 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 (QICA) and superior mesenteric artery (QSM) 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

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<th>Baseline</th>
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<td>236 ± 52‡</td>
<td>213 ± 42‡</td>
<td>191 ± 45‡</td>
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<td>324 ± 56</td>
<td>327 ± 52</td>
<td>324 ± 51</td>
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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)/QSMa, and (MAP – RAP)/Qica, 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 (SO2) (OSM 3; Radiometer), corrected for species.

Systemic Do2 (Do2sys; milliliters per minute per kilogram body weight) was calculated as:

\[ \text{CI} \times \text{arterial O2 content}, \]

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:

\[ ((1.31 \times [\text{Hb}] \times \text{Sao2}) + (0.003 \times \text{Pao2})) \times 0.01, \]

where Pao2 is arterial oxygen partial pressure and Sao2 is arterial oxygen saturation. Systemic oxygen consumption (V02sys; milliliters per minute per kilogram body weight) was calculated as:

\[ \text{CI} \times (\text{arterial} – \text{mixed venous O2 content difference}). \]

The systemic O2ER (O2ERsys; percent) was calculated as:

\[ (\text{arterial} – \text{mixed venous O2 content difference})/(\text{arterial O2 content}). \]

In a similar way, the intestinal Do2 (Do2sma), V02 (V02sma), and O2ER (O2ERSMA) were calculated. Measurement of the internal jugular venous oxygen content allowed the calculation of the arteriovenous oxygen content difference, and thereby the O2ER of the brain20–22 (O2ERica) was calculated as:

\[ (\text{arterial} – \text{internal jugular venous O2 content difference})/(\text{arterial O2 content}). \]

Microvascular Oxygen Partial Pressure Measurements

The μP02 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 μP02 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 (DO2SYS) decreased with the onset of hemodilution, whereas the systemic oxygen consumption (VO2SYS) decreased after the final hemodilution step. Systemic oxygen extraction ratio (O2ER 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 compared with baseline; #P < 0.05 HD versus previous.

**Experimental Procedure**

After preparation and a stabilization period of at least 30 min, two baseline measurements were made during a 3-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 HAESterial 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 VO2 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, FIO2 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 FIO2 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 VO2 and the μPO2 of the intestinal serosa and mucosa and the cerebral cortex. From plots of hematocrit against VO2SYS and μPO2, it was possible to determine the points at which VO2 or μPO2 became dependent on the hematocrit with further hemodilution. These points were determined for each animal separately by the intersection of
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; SaO₂ = arterial O₂ saturation; PaO₂ = arterial tension O₂; CaO₂ = arterial O₂ content; PaCO₂ = arterial partial pressure of CO₂; pH = arterial pH; Lac art = arterial lactate concentration; SvO₂ = mixed venous O₂ saturation; PvO₂ = mixed venous partial pressure of O₂; pHv = mixed venous pH; Lac mix = mixed venous lactate concentration.

### 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, $\text{DO}_{2\text{SYS}}$ decreased with the onset of hemodilution. The $\text{O}_2\text{ERSYS}$ increased, and as a result the $\text{VO}_{2\text{SYS}}$ 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 $\text{PO}_2$ and $\text{SO}_2$ 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 $\text{DO}_{2\text{SYS}}$, despite the decrease in CI. The $\text{O}_2\text{ERSYS}$ decreased significantly following hyperoxia, and $\text{VO}_{2\text{SYS}}$ was not restored. Mixed venous $\text{PO}_2$ and $\text{SO}_2$ 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
DO$_{2 SYS}$ and VO$_{2 SYS}$, 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 (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 Q$_{SMA}$, resulting in a progressive decrease in DO$_{2 SMA}$. After exchange of 60 ml/kg (corresponding hematocrit, 9.9%), VO$_{2 SMA}$ was decreased from baseline, whereas O$_2$ER$_{SMA}$ increased from 21 ± 7% at baseline to 46 ± 9% after the final hemodilution step (fig. 2).

Baseline values for the carotid blood flow (Q$_{ICA}$; fig. 3) and the corresponding vascular resistance (table 1) were comparable for both groups. 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$_2$ER$_{ICA}$ (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 Q$_{SMA}$ after hemodilution. The DO$_{2 SMA}$ increased slightly but not significantly, and VO$_{2 SMA}$ 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 Q$_{SMA}$ decreased, resulting in a decrease in DO$_{2 SMA}$ but not in VO$_{2 SMA}$. The change in O$_2$ER$_{SMA}$ 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 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.

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**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 (Q$_{SMA}$) did not change during hemodilution. Superior mesenteric artery oxygen delivery (DO$_{2 SMA}$) decreased with the onset of hemodilution; VO$_{2 SMA}$ decreased after the third hemodilution step. Superior mesenteric artery oxygen extraction ratio (O$_2$ER$_{SMA}$) increased progressively during the experiment. Hyperoxia significantly decreased Q$_{SMA}$ and DO$_{2 SMA}$ in the control group and O$_2$ER$_{SMA}$ 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.

**Fig. 3.** Internal carotid artery blood flow (Q$_{ICA}$) and cerebral oxygen extraction ratio (O$_2$ER$_{ICA}$) 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). Q$_{ICA}$ increased after the first hemodilution step, O$_2$ER$_{ICA}$ 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.

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Microvascular Oxygen Partial Pressure Measurements

Microvascular and regional venous PO₂ measurements are shown in figure 4. Baseline measurements were similar for the hemodilution and the control groups. The μPO₂ 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 μPO₂ (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 μPO₂ of the cerebral cortex (26 ± 3 mmHg at baseline) demonstrated a similar behavior as the mucosal μPO₂ and was also decreased after the third hemodilution step. μPO₂ measurements in the control groups did not change in time.

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>20 ml</th>
<th>40 ml</th>
<th>60 ml</th>
<th>90 ml</th>
<th>Hyperoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht (%)</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.3 ± 3.0</td>
<td>17.0 ± 2.1†‡</td>
<td>12.8 ± 1.3†††</td>
<td>9.9 ± 1.1†††</td>
<td>7.6 ± 1.2†††</td>
<td>8.0 ± 1.4†††</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>25.7 ± 2.8</td>
<td>25.1 ± 2.8</td>
<td>25.1 ± 1.5</td>
<td>24.9 ± 1.2</td>
<td>27.2 ± 1.4</td>
</tr>
<tr>
<td>Smvo₂ (%)</td>
<td>H</td>
<td>80 ± 8</td>
<td>74 ± 9</td>
<td>69 ± 9*</td>
<td>64 ± 10*</td>
<td>58 ± 9*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>76 ± 6</td>
<td>73 ± 6</td>
<td>70 ± 4</td>
<td>72 ± 5</td>
<td>72 ± 6</td>
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<tr>
<td>pHmv</td>
<td>H</td>
<td>7.45 ± 0.03</td>
<td>7.43 ± 0.03</td>
<td>7.40 ± 0.03†††</td>
<td>7.39 ± 0.03*</td>
<td>7.35 ± 0.04†‡</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>7.45 ± 0.03</td>
<td>7.43 ± 0.01</td>
<td>7.42 ± 0.01</td>
<td>7.42 ± 0.02</td>
<td>7.41 ± 0.02</td>
</tr>
<tr>
<td>Lac mes (mM)</td>
<td>H</td>
<td>1.80 ± 0.25</td>
<td>1.55 ± 0.41</td>
<td>—</td>
<td>—</td>
<td>1.50 ± 0.47</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1.72 ± 0.36</td>
<td>1.67 ± 0.38</td>
<td>—</td>
<td>—</td>
<td>1.51 ± 0.32</td>
</tr>
<tr>
<td>SjvO₂ (%)</td>
<td>H</td>
<td>70 ± 10</td>
<td>66 ± 8</td>
<td>66 ± 6</td>
<td>61 ± 8</td>
<td>57 ± 8*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>73 ± 6</td>
<td>68 ± 4</td>
<td>70 ± 5</td>
<td>70 ± 6</td>
<td>73 ± 9</td>
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<tr>
<td>pHjv</td>
<td>H</td>
<td>7.42 ± 0.04</td>
<td>7.42 ± 0.02</td>
<td>7.40 ± 0.02</td>
<td>7.37 ± 0.02*</td>
<td>7.35 ± 0.04*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>7.44 ± 0.04</td>
<td>7.42 ± 0.02</td>
<td>7.43 ± 0.01</td>
<td>7.42 ± 0.02</td>
<td>7.41 ± 0.02</td>
</tr>
<tr>
<td>Lac jug (mM)</td>
<td>H</td>
<td>2.19 ± 0.43</td>
<td>2.15 ± 0.41</td>
<td>—</td>
<td>—</td>
<td>2.39 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>2.16 ± 0.41</td>
<td>2.44 ± 0.48</td>
<td>—</td>
<td>—</td>
<td>2.03 ± 0.49</td>
</tr>
</tbody>
</table>

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; Smvo₂ = mesenteric venous O₂ saturation; pHmv = mesenteric venous pH; Lac mes = mesenteric venous lactate concentration; SjvO₂ = jugular venous O₂ saturation; pHjv = jugular venous pH; Lac jug = jugular venous lactate concentration.
In the hemodilution group, hyperoxia increased both the serosal and the mucosal $\mu$Po$_2$; the mucosal $\mu$Po$_2$ was even restored to baseline values. The cerebral cortex $\mu$Po$_2$ 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 $\text{V}O_2$ and intestinal and cerebral $\mu$Po$_2$ measurements are shown in figure 5. $\text{V}O_2\text{SYS}$ (fig. 5A) started to decrease with hemodilution at an average hematocrit of 13.7 $\pm$ 3.5%. In the intestines, the critical hematocrit for the intestinal mucosa (fig. 5B) was 11.4 $\pm$ 2.6%, whereas the serosal $\mu$Po$_2$ (fig. 5C) started to decrease with hematocrit already at an average value of 16.9 $\pm$ 4.2%. The $\mu$Po$_2$ in the cerebral cortex (fig. 5D) displayed a similar behavior as the intestinal mucosa and $\text{V}O_2\text{SYS}$ and started to decrease with hematocrit at an average value of 12.1 $\pm$ 3.1%. The critical hematocrit values for the mucosal and cerebral $\mu$Po$_2$ and $\text{V}O_2\text{SYS}$ were not significantly different; compared with the serosal $\mu$Po$_2$, the critical hematocrit of the latter was found to be significantly higher.

**Fig. 5.** (A) Critical levels of hemodilution for the systemic oxygen consumption ($\text{V}O_2$), calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 13.7 $\pm$ 3.5%. (B) Critical levels of hemodilution for the mucosal microvascular oxygen partial pressure ($\mu$Po$_2$), calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 11.4 $\pm$ 2.6%. (C) Critical levels of hemodilution for the serosal $\mu$Po$_2$, calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 16.9 $\pm$ 4.2%, which was significantly higher than the critical hematocrit values of the mucosal and cerebral $\mu$Po$_2$ and systemic $\text{V}O_2$. (D) Critical levels of hemodilution for the cerebral cortex $\mu$Po$_2$, calculated for the hematocrit. The critical values were determined for each animal separately, resulting in an average critical hematocrit of 12.1 $\pm$ 3.1%.
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 pH measurements did not change in the control group. In the hemodilution group, the arterial pH decreased significantly after the final hemodilution step. The mixed venous pH did not change, but the mesenteric venous pH decreased after the second step and the jugular venous pH 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 $\mu PO_2$, and the intestinal mucosal $\mu PO_2$ became impaired at the same stage during hemodilution, whereas the intestinal serosal $\mu PO_2$ 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 $Q_{SMA}$ remained constant. Despite the redistribution of blood flow, systemic as well as intestinal $V_02$ 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 $V_02$ has been reported in previous studies as well. 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 DO2.29 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 viscosity36–38; increased nitric oxide activity should not be involved in this process.39

Although the VO2SMA and the mucosal μPO2 were preserved until a hematocrit of ±11.0%, the serosal μPO2 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.14,34 A redistribution of intraorgan blood flow during hemodilution has been shown to occur in the heart8,40,41 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 pH 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 DO2 could not be demonstrated during hemodilution in conscious animals and humans.44–46

The increase in Fio2 did not improve systemic or intestinal VO2 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 PO2 values far more than the μPO2 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 flow47) 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 VO2SMA and the cerebral and intestinal mucosal μPO2, whereas the intestinal O2ER increased to a greater extent than the cerebral O2ER, 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 μPO2 decreased at an earlier stage than the mucosal μPO2, 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 VO2. The increased regional venous PO2 values in combination with the decreased O2ER indicate that the increased amount of physically dissolved oxygen was shunted to the venous side of the organ vascular beds during severe hemodilution.

References

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