Heart, kidney, and intestine have different tolerances for anemia

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Organ systems do not respond uniformly to changes in systemic oxygen delivery because of global and local redistributive mechanisms. We hypothesized that progressive hemodilution would evoke a different response in the microvascular oxygenation of the heart compared with kidney and gut. To evaluate this hypothesis, we studied the effect of stepwise isovolemic hemodilution on systemic hemodynamic and oxygenation parameters as well as the relation between systemic hematocrit (Ht) and microvascular PO_2 (μPO_2) in heart, kidney, and intestines in an anesthetized and mechanically ventilated rat model.

Baseline conditions were similar in the hemodilution group and in the control group. In the hemodilution group, Ht was diminished from 46.6 ± 3.8% to 7.0 ± 1.8% (mean ± standard deviation (SD)). This group had no effect on measured hemodynamics; only when Ht fell below 10% did blood pressure start to decrease. The μPO_2 values in heart, kidney, and intestines did not respond uniformly. Renal μPO_2 (56 ± 10 mm Hg at baseline) started to decrease at a Ht of 38.5 ± 8.6%, whereas intestinal μPO_2 (59 ± 6 mm Hg at baseline) did not start to decrease until Ht reached 17.4 ± 7.1%. Finally, cardiac μPO_2 (40 ± 6 mm Hg at baseline) decreased only in the ultimate stage of the experiment at Ht of 8.7 ± 3.5%.

Based on these observations, we conclude that the regulation of microvascular oxygenation during progressive anemia is specific for each organ system. The relation between these observations and organ function and damage needs to be determined. (Translational Research 2008;151:110-117)

Abbreviations: μPO_2 = microvascular PO_2; DO_2 = oxygen delivery; Hb = hemoglobin; Ht = hematocrit; MAP = mean arterial pressure; P_aO_2 = arterial PO_2; P_aCO_2 = arterial PCO_2; P_{puls} = pulse pressure; SD = standard deviation; VO_2 = oxygen consumption

Hemodilution can be used to delay the need for blood transfusion during surgery. It is standard practice during cardiopulmonary bypass and occurs during fluid resuscitation. Although the O_2-carrying capacity of the blood is reduced with dilution of the blood components, the O_2 demand of the body is met by increases in cardiac output and O_2 extraction. However, when the systemic oxygen delivery (DO_2) falls below a critical point, these compensatory mechanisms become insufficient and systemic oxygen consumption (VO_2) becomes dependent on supply.[1-4]

Large differences exist in the tolerance of different organs for hemodilution, which occurs partly because of systemic redistribution of the decreasing O_2 supply in favor of vital organs[5-7] and partly because of differing intrinsic organ responses.[8-11] However, simultaneous relations that involve hematocrit (Ht) and microvascular PO_2 (μPO_2) measurements in different organs have not yet been determined during hemodilution. Because the μPO_2 can be considered to reflect the balance between regional O_2 supply and demand,[12,13] it

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AT A GLANCE COMMENTARY

Background

The regulation of tissue oxygenation during progressive anemia is specific for each organ system and is a product of global and local redistribution of the decreased systemic oxygen supply, which is reflected by changes in the microvascular oxygenation of the organ during hemodilution.

Translational Significance

Based on our results, we conclude that moderate hemodilution evokes an active response in the kidney, which leads to a direct change in the O_2 supply–demand relation. The intestines and the heart are less sensitive to low hemoglobin levels: In particular, cardiac O_2 supply–demand is maintained during severe anemia.

can be assumed that a decrease in μPO_2 might precede impairment of regional VO_2. Therefore, simultaneous determination of these Ht–μPO_2 relations for different organs, including a vital organ as heart or brain, would provide more detailed information on the functional effects of redistribution during isovolemic hemodilution.

The current study was designed to determine and compare the Ht levels at which the μPO_2 values in the heart, kidney, and intestines could not be preserved any longer and became dependent on oxygen delivery during severe normovolemic hemodilution in an anesthetized rat model.

MATERIALS AND METHODS

Animals. The protocol of the current 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 12 male Wistar rats with a mean [± standard deviation (SD)] bodyweight of 332 ± 30 g.

Experimental preparation. The rats were anesthetized with an intraperitoneal injection of a mixture of 90-mg kg^{-1} ketamine, 0.5-mg kg^{-1} medetomidine, and 0.05-mg kg^{-1} atropine. Anesthesia was maintained with 50-mg kg^{-1} h^{-1} ketamine (i.v.). To compensate for fluid loss, crystalloid solution was administered intravenously at a rate of 15 mL kg^{-1} h^{-1}. Body temperature was measured with a thermocouple placed in the rectum and was maintained at 37 ± 0.5°C with a heating pad under and a warming lamp above the animal. Tracheotomy was performed, and a PVC tube (Ch 6) was inserted into the trachea to enable mechanical ventilation with a mixture of 30% oxygen and 70% nitrogen. A capnometer (Capstar-100; CWE, Inc., Ardmore, Pa) was used to measure end-tidal PCO_2. This information was used to adjust ventilator settings to maintain an arterial PCO_2 between 35 and 40 mm Hg.

A polyethylene catheter (outer diameter 0.9 mm) was inserted into the right jugular vein for intravenous administration of drugs and fluids. The tip of the catheter was advanced near the right atrium for central venous blood sampling. A similar catheter was placed into the right carotid artery and was connected to a pressure transducer for continuous monitoring of arterial blood pressure and heart rate. Catheters of the same size were placed into both the right femoral artery and the vein for withdrawal of blood and administration of fluid. After midline laparotomy, a PVC catheter (outer diameter 0.9 mm) was placed in the urinary bladder to prevent distension of the bladder wall during the experiment and to monitor urine production. The surface of the right kidney was exposed by careful manipulation of the intestines. A midline thoracotomy was performed to gain access to the heart. A thermocouple was placed on the intestinal surface, and all exposed organ surfaces were covered with plastic foil to prevent evaporative fluid loss.

Hemodynamic and blood gas measurements. Systolic and diastolic arterial pressures were measured in the carotid artery. Mean arterial pressure (MAP) was calculated as MAP (mm Hg) = diastolic pressure + (systolic pressure − diastolic pressure) / 3. The amplitude of the arterial blood pressure was calculated as P_{puls} = systolic pressure − diastolic pressure. Blood samples of 0.2 mL each were collected and replaced with the same volume of a pasteurized protein solution (PPS; CLB, Amsterdam, the Netherlands). At each measurement point, an arterial sample was taken from the femoral artery and a central venous sample was taken from the jugular venous catheter. The samples were used to determine blood gas values (ABL505; Radiometer, Copenhagen, Denmark), as well as Ht, hemoglobin (Hb) concentration, and Hb oxygen saturation (OSM 3; Radiometer, Copenhagen, Denmark).

μPO_2 measurements. The μPO_2 was measured in heart, kidney, and intestines 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 related quantitatively to the oxygen concentration.[14,15] Pd-meso-tetra(4 carboxy-phenyl)porphine (Porphyrin Products, Logan, Utah) is coupled to human serum albumin to form a large molecular complex that, when injected intravenously, is confined mainly to the vascular compartment.[16,17] One milliliter of a 4-mmol/L Pd-porphyrin solution was administered, which corresponds with a dosage of 12-mg/kg bodyweight. The μPO_2 measurements were made with optical fibers for the transmission of excitation and emission light, which is 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.[18] It was found that simultaneous PO_2 measure-

Table I. Systemic effects of severe isovolemic hemodilution in anesthetized rats

	Baseline 1	Baseline 2	H1	H2	H3	H4
Ht [%]						
H	46.6 ± 3.8	46.9 ± 4.0	27.8 ± 6.2*†	17.3 ± 4.1*†‡	9.2 ± 1.8*†‡	7.0 ± 1.8†*
C	43.4 ± 2.7	43.3 ± 1.0	41.2 ± 2.0	39.4 ± 1.7†	37.9 ± 1.4†	36.5 ± 1.2†
[Hb] [g/dL]						
H	15.1 ± 1.2	15.2 ± 1.4	8.9 ± 2.1†*	5.4 ± 1.4*†‡	2.7 ± 0.6*†‡	1.9 ± 0.5*†
C	14.1 ± 0.9	14.1 ± 0.3	13.4 ± 0.7	12.9 ± 0.8†	12.2 ± 0.3†	11.9 ± 0.3†
MAP [mm Hg]						
H	108 ± 9	108 ± 10	101 ± 8	98 ± 7	63 ± 11*†‡	41 ± 14*†‡
C	106 ± 8	110 ± 12	106 ± 7	103 ± 8	102 ± 5	99 ± 4
P_{puls} [mm Hg]						
H	19 ± 5	20 ± 8	22 ± 6*	30 ± 8*	32 ± 13†*	19 ± 10‡
C	13 ± 5	12 ± 3	10 ± 2	14 ± 8	16 ± 5	14 ± 5
HR [b/min]						
H	220 ± 24	197 ± 16	205 ± 21	210 ± 24	216 ± 33	214 ± 27
C	211 ± 10	222 ± 13	219 ± 20	215 ± 31	218 ± 13	220 ± 23
Urine [norm.]						
H	1.0 ± 0.0	1.7 ± 0.2	2.0 ± 0.2	2.7 ± 0.4†‡	3.3 ± 0.5†	3.5 ± 0.6†
C	1.0 ± 0.0	1.2 ± 0.1	1.6 ± 0.1†	2.0 ± 0.2†‡	2.5 ± 0.2†‡	2.7 ± 0.2†

Abbreviations: C, control group (n = 3); H, hemodilution group (n = 9); HR, heart rate.
Note: Values represent mean ± SD.
*$P < 0.05$ vs control.
†$P < 0.05$ vs baseline (1 and 2).
‡$P < 0.05$ vs previous.

ments 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.[18] Therefore, these results allowed us to determine the fiberoptic measurement of PO_2 as the measurement of μPO_2. Fiberoptic measurements of μPO_2 incorporate blood vessels under the fiber over an area of approximately 1 cm^2 to a penetration depth of about 0.5 mm.[17,19] Because 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 current study, a multifiber phosphorimeter was used, with 3 separately operated optical fibers. The use of this device allowed us to measure the μPO_2 in heart, kidney, and gut simultaneously.

Experimental procedure. After surgery and stabilization, 2 baseline measurements were made during a 1-h period. Subsequently, the animals were assigned to either a hemodilution (n = 9) or a time-matched control group (n = 3), in which identical measurements were made at corresponding time intervals, but no hemodilution was performed. Isovolemic hemodilution was accomplished by withdrawal of blood from the femoral artery and simultaneous administration through the femoral vein of pasteurized protein solution at the same rate. The oncotic pressures of PPS and rat blood were determined, and it was found that the protein solution is slightly hyperoncotic compared with rat blood (oncotic pressures of 14.5 ± 0.4 and 12.7 ± 0.6 mm Hg for PPS and rat blood, respectively), and it is therefore suitable for isovolemic hemodilution. Infusion/withdrawal occurred at a rate of 20 mL/h using a double syringe pump (Harvard 33; Harvard Apparatus, South Natick, Mass), and it did not cause any undesired hemodynamic reactions in this model. Four dilution steps were made: from baseline to a hematocrit of approximately 25% (H1), to 15% (H2), to 10% (H3), and finally to 5% to 10% (H4). A 15-min stabilization period followed each dilution step before measurements were made. The experiments were terminated after measurement H4 by administration of an overdose of pentobarbital (60 mg intravenous). Final μPO_2 measurements were made postmortem.

Statistical analysis. Values are reported as mean ± SD. Data were analyzed using analysis of variance for repeated measurements. When appropriate, post hoc analyses were performed with the Student–Newman–Keuls test. *P* values less than 0.05 were considered significant. The hemodilution and the control group were compared using the Mann–Whitney test. The effect of hemodilution on the different organ μPO_2 values was determined using plots of Ht against μPO_2. From these plots, it was possible to determine the points at which the μPO_2 of heart, kidney, and intestines became dependent on hematocrit with additional hemodilution. These points were determined for each animal separately, by the intersection of the two best-fit regression lines, as determined by a least sum-of-squares technique. Postmortem μPO_2 measurements were not included in the fit procedure.

RESULTS

Systemic parameters. Data are summarized in Tables I and II. Baseline measurements in the hemodilution and control groups were not significantly different. In the hemodilution group, systemic Ht decreased from 46.6 ± 3.8% at baseline 1 to 7.0 ± 1.8% at H4. A

Table II. Arterial and central venous blood gas analysis during severe isovolemic hemodilution in anesthetized rats

	Baseline 1	Baseline 2	H1	H2	H3	H4
P_aO_2 [mm Hg]						
H	147 ± 15	150 ± 19	151 ± 17	148 ± 17	165 ± 26	191 ± 23†‡
C	169 ± 16	160 ± 23	187 ± 15	188 ± 15	209 ± 19	206 ± 17
S_aO_2 [%]						
H	98.1 ± 1.2	97.5 ± 2.5	97.4 ± 1.5*	98.1 ± 1.4	99.7 ± 0.5	99.7 ± 0.5
C	99.7 ± 0.6	98.8 ± 1.2	99.8 ± 0.3	99.8 ± 0.3	99.5 ± 0.8	99.7 ± 0.5
P_aCO_2 [mm Hg]						
H	37 ± 2	38 ± 5	39 ± 4	34 ± 4	29 ± 6†‡	21 ± 5*†‡
C	36 ± 5	38 ± 3	39 ± 2	36 ± 4	38 ± 5	36 ± 2
pH_a						
H	7.35 ± 0.02	7.35 ± 0.02	7.36 ± 0.03	7.35 ± 0.04	7.34 ± 0.05	7.36 ± 0.12
C	7.36 ± 0.04	7.34 ± 0.06	7.35 ± 0.06	7.36 ± 0.05	7.32 ± 0.03	7.33 ± 0.03
S_vO_2 [%]						
H	70.5 ± 8.7	65.6 ± 7.2	54.0 ± 9.0†	39.3 ± 9.7*†‡	33.2 ± 10.5*†	23.5 ± 10.6*†‡
C	67.6 ± 5.0	64.1 ± 5.8	64.3 ± 4.0	62.3 ± 6.5	58.9 ± 6.2	55.9 ± 3.1

Abbreviations: C, control group (n = 3); H, hemodilution group (n = 9); pH_a, arterial pH; S_aO_2, arterial Hb O_2 saturation; S_vO_2, central venous hemoglobin O_2 saturation.
Note: Values represent mean ± SD.
*$P < 0.05$ vs control.
†$P < 0.05$ vs baseline (1 and 2).
‡$P < 0.05$ vs previous.

similar decrease was found for the Hb concentration (from 15.1 ± 1.2 g dL^{-1}at baseline 1 to 1.9 ± 0.5 g dL^{-1}at H4). Because of blood sampling and subsequent volume correction, a small but significant degree of hemodilution took place in the control group: Ht decreased from 43.4 ± 2.7% at baseline 1 to 36.5 ± 1.2% at H4, and Hb decreased from 14.1 ± 0.9 g dL^{-1} at baseline 1 to 11.9 ± 0.3 g dL^{-1} at H4.

Initially, the MAP was not affected by hemodilution. However, when Ht fell below 10% at H3, MAP decreased significantly to 63 ± 11 mm Hg and to 41 ± 14 mm Hg at H4. Blood pressure did not change in the control group. During hemodilution, pulse pressure (P_{puls}) increased significantly compared with the control group, from 19 ± 5 mm Hg at baseline 1 to 32 ± 13 mm Hg at H3. At H4, P_{puls} returned to baseline values. P_{puls} did not change significantly in the control group. The heart rate was not affected by hemodilution and remained in the range of 200 – 220 beats/minute in both the hemodilution and the control group. The urine production, which was normalized to the start of the experiment, was similar in both groups and increased significantly throughout the experiment.

Arterial PO_2 (P_aO_2) demonstrated a small increase during the experiment in both groups. This increase became significant in the hemodilution group only at H4. The arterial Hb O_2 saturation was stable in both groups. The central venous Hb O_2 saturation decreased progressively with the onset of hemodilution from 70.5 ± 8.7% at baseline 1 to 23.5 ± 10.6 at H4. This parameter did not change significantly in the control group. The arterial pH remained at baseline levels until H4 in both groups. At H3, which is similar to the MAP, the arterial PCO_2 (P_aCO_2) in the hemodilution group (37 ± 2 mm Hg at baseline 1) decreased to 29 ± 6 mm Hg and to 21 ± 5 mm Hg at H4. In the control group, P_aCO_2 remained between 35 and 40 mm Hg throughout the experiment.

μPO_2 measurements. Data are summarized in Figs 1 and 2. Baseline measurements in the hemodilution and control groups were not significantly different. μPO_2 values of the heart, kidney, and intestines did not respond uniformly to isovolemic hemodilution. The intestinal μPO_2 (59 ± 6 mm Hg at baseline 1) did not change until the Ht was decreased below 20% at H2. At this point, intestinal μPO_2 fell to 44 ± 9 mm Hg and decreased with additional hemodilution to 9 ± 5 mm Hg at H4, which was not significantly different from the postmortem value of 4 ± 2 mm Hg. The critical Ht value for the intestinal μPO_2 was determined at a Ht value of 17.4 ± 7.1%.

In the kidney, the μPO_2 (56 ± 10 mm Hg at baseline 1) decreased immediately with the onset of hemodilution. At H3 (Ht 9.2 ± 1.8%), renal μPO_2 was 7 ± 5 mm Hg, which was in the same range as the postmortem value of 2 ± 1 mm Hg. The critical Ht value where the renal μPO_2 started to decline was determined at a Ht value of 38.5 ± 8.6%.

In contrast to the intestinal and renal μPO_2 values, the cardiac μPO_2 (40 ± 6 mm Hg at baseline 1) was

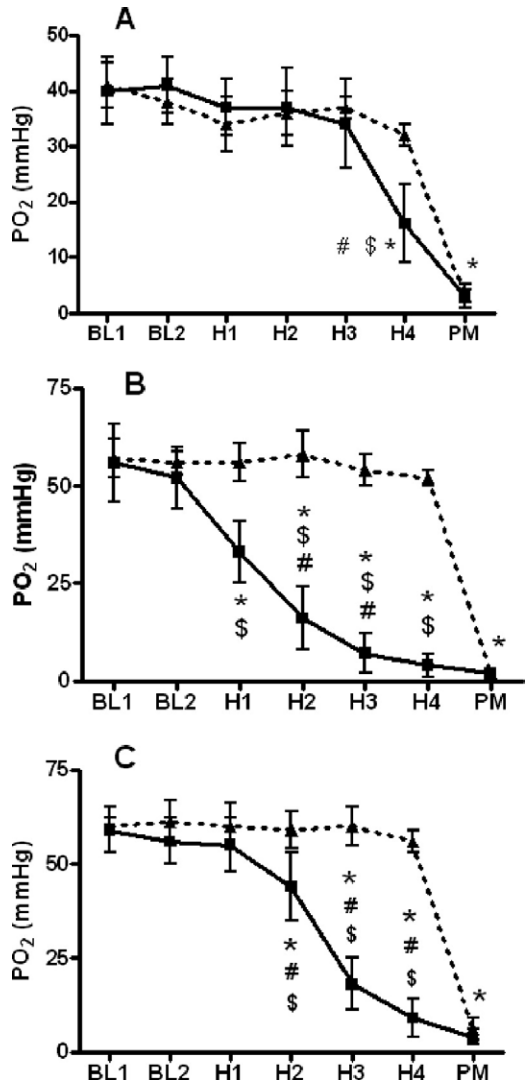

Fig 1. Microvascular PO_2 measurements during hemodilution. **A**, cardiac μPO_2. **B**, renal μPO_2. **C**, intestinal μPO_2. Straight line: hemodilution group (n = 9); dashed line: control group (n = 3). Postmortem measurements were made 15 min after the animals were killed. $*P < 0.05$ vs baseline (1 and 2), $\#P < 0.05$ vs previous. $\$P < 0.05$ vs control. Values represent mean ± SD.

affected very little by hemodilution. Only in the final stage of the experiment, when Ht fell below 10%, was a significant decrease to 16 ± 7 mm Hg observed. This value was still above the postmortem measurement of 3 ± 1 mm Hg. Cardiac μPO_2 declined precipitously below a Ht value of 8.7 ± 3.5%.

The μPO_2 measurements in the control groups were stable throughout the experiments in all 3 organs. Only after termination of the experiment did the μPO_2 values decrease to very low values, which is similar to the postmortem values in the hemodilution group.

DISCUSSION

The main finding of the current study is that the μPO_2 values of heart, kidney, and intestines responded differently to severe isovolemic hemodilution. The different organ systems had different critical Ht values below which μPO_2 declined markedly with progressive hemodilution, which suggests organ-specific tolerances for anemia.

The amount of physically dissolved oxygen in the microvessels, the μPO_2, is a driving force for the diffusion of oxygen into the tissue and can in general be assumed to reflect the balance between local O_2 supply and demand. Thus, when O_2 supply decreases relative to demand, the latter is maintained by increased extraction, which leads to lower μPO_2 levels. However, this hypothesis assumes that blood flow is either a constant factor or is related directly to tissue VO_2. Although we have no information on blood flow in our experiment, our results clearly suggest that during hemodilution the relation among global organ DO_2, tissue VO_2, and μPO_2 is not uniform and is determined at a regional level.

In general, the kidney is not demanding the high blood flow it gets based on its O_2 demand at rest. Nevertheless, the μPO_2 of the kidney demonstrated the lowest tolerance for hemodilution, as it decreased immediately with the onset of hemodilution. According to our hypothesis, this would be the result of decreased O_2 supply and/or increased O_2 demand. This hypothesis was confirmed by the results of Johannes et al[11], who demonstrated that with progressive hemodilution renal DO_2 slowly decreased (despite an increase in blood flow), whereas VO_2 actually increased. Simultaneously, μPO_2 levels fell immediately with hemodilution, as happened in our experiment. Based on these observations, we hypothesized that in our experiment Ht becomes "critical" for the renal μPO_2 at about 38%, which is not because of decreased O_2 content or impaired blood flow but is because of an enhanced VO_2.

However, the reasons for the immediate increase in renal VO_2 during hemodilution remain speculative. In response to a fall in blood viscosity or MAP, energy-consuming adaptive mechanisms in the kidney might have been activated to increase sodium and water reabsorption.[20] On the other hand, we did not observe reduced urine output during hemodilution. Additionally, increased shunting of oxygen from cortical arterioles to venules might have contributed to the sudden decrease in renal μPO_2.[21,22]

In comparison, the intestinal μPO_2 observed in our experiment was better preserved and started to decrease only at a Ht of 17.4%. In a previous study, we found a similar critical Ht for both the intestinal microvascular

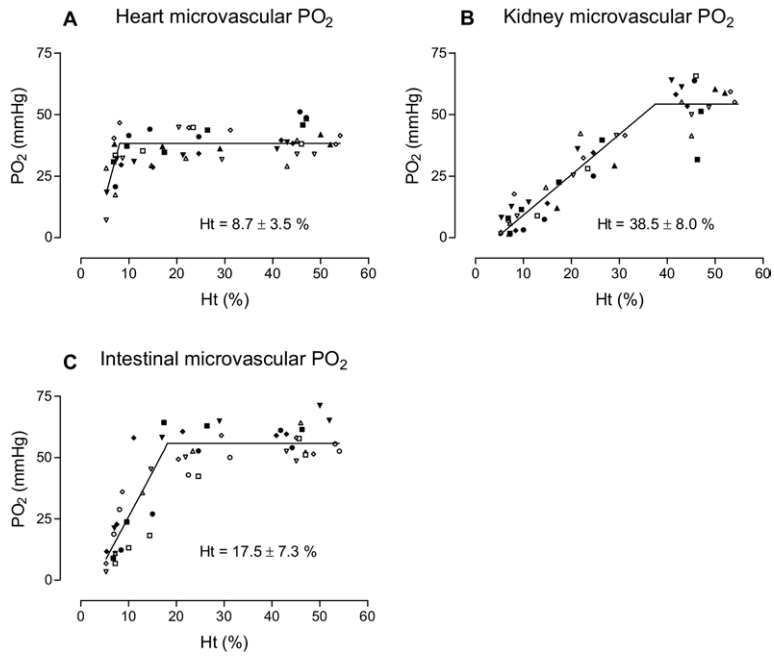

Fig 2. Ht–μPO_2 relations during hemodilution. **A**, The relation Ht–μPO_2 for the heart. **B**, The relation Ht–μPO_2 for the kidney. **C**, The relation Ht–μPO_2 for the intestines. Relations were determined for each animal separately and are presented as mean ± SD. Data that originated from one animal are represented by identical symbols.

oxygenation and VO_2.[13] At this point, intestinal VO_2 became supply dependent, which resulted in a linear relation with intestinal μPO_2 during progressive hemodilution. In addition, shunting of oxygen through the microcirculation was observed to contribute to the decrease in μPO_2.

It must be noted that the size of the rat small intestine did not allow us to distinguish between a mucosal and a serosal μPO_2. In a porcine hemodilution model, it has been observed that serosal μPO_2 decreased at greater Ht levels than mucosal μPO_2 and systemic VO_2.[8] This finding was explained by redistribution of the intestinal blood flow within the intestinal wall (ie, the serosa and the mucosa).[10] The intestinal μPO_2 values in the current study must be considered to be the admixture of different μPO_2 values across the layers of the intestinal wall. The limitations of the rat model did not allow us to evaluate the blood flow in separate intestinal layers. Finally, it must be kept in mind that during the experiment intestinal metabolism was at rest and that, in contrast with the kidney, intestinal O_2 demand remained low. As a result, the critical Ht was lower (ie, the tolerance for anemia was greater).

When we examined the heart, we found that μPO_2 in this organ was affected very little by hemodilution. Only when a Ht of 8.7% had been reached could a change in μPO_2 be observed. Apparently, the oxygenation of the heart is maintained even under severely compromising circumstances. As indicated by the μPO_2 values in the different organs throughout this experiment, either the decreasing amount of systemic available O_2 is redistributed in favor of the oxygenation of the heart and/or the heart can match O_2 supply and demand until the final stage of hemodilution when Ht decreased below 8%. This result was reflected in the hemodynamic measurements. Although the heart rate showed no change at H4, the P_{puls} (which actually increased until H3) suddenly decreased and MAP also decreased to 41 mm Hg. Similarly, $P_aO_2$increased and the P_aCO_2 decreased to 21 mm Hg at H4. This state of circulatory collapse was most likely the result of myocardial failure: Because of insufficient myocardial oxygen supply, the heart could no longer increase its output to maintain blood pressure in a vascular system where vasoconstriction was impaired by generalized vasodilation needed for critical tissue oxygen supply. As a result, the increased ventilation–perfusion ratio must have been caused by decreased pulmonary perfusion as the ventilator setting was not changed. Based on P_{puls}, urine production, the use of a slightly hyperoncotic protein solution and a slight increase in total bodyweight during the experiment hypovolemia was excluded as a potential cause for hypotension in the hemodilution group. A similar decline in MAP with marked isovolemic hemodilution has been observed in

other experiments not only with rats[23] but also with dogs.[7]

Only when the activity of the heart was terminated with pentobarbital did the cardiac μPO_2 fall to 3 mm Hg, which is comparable with the values renal and intestinal μPO_2 had reached at an earlier stage. Thus, in contrast with the other organs, the cardiac tissue was provided with O_2 even at an extreme level of hemodilution as long as some blood flow was maintained. This finding is in agreement with the results of prior investigations, which demonstrated that below a Ht of 10%, only the O_2 flux to the heart was maintained compared with brain, kidney, stomach, small intestine, and skin[5] or total body.[24] Again it must be realized that the measurement of the myocardial μPO_2 in the current experiment might have been influenced by redistribution of the blood flow within the organ; hemodilution below a Ht level of 20% has been shown to cause a decrease in the ratio of endocardial versus epicardial blood flow.[5,25,26]

The major limitation of our study is the lack of flow measurements: We can only speculate about any changes in (distribution of) blood flow at the specific critical Ht values. In general, the response to hemodilution is vasodilation to compensate for the decreased arterial oxygen content. The effect on total organ blood flow seems to depend on the oxygen extraction reserve of the tissue. For instance, the heart has little capacity to increase O_2 extraction, and it is therefore dependent on its vasodilator reserve to maintain VO_2. It can be assumed that here the maximum vasodilatory reserve coincides with the critical Ht, at which point μPO_2 decreases. The intestines, on the other hand, have (at rest) a much larger capacity to increase O_2 extraction. Intestinal blood flow does not increase that much during hemodilution, and vasodilation mainly occurs at a very regional level in the form of an increased capillary density. Here, the critical Ht seems not to coincide as much with the tissue's maximum vasodilator reserve as with the limits of extraction capacity. Finally, the relation between blood flow and O_2 demand in the kidney during hemodilution is more complicated. As discussed, we explained the simultaneous increase in renal blood flow and decrease in μPO_2 by increased renal metabolism. It is unclear how this relates to the critical Ht values.

The exact mechanisms of the global and local redistribution of O_2 supply are largely unknown. Possible mechanisms that could account for systemic and/or local redistribution could include increased sympathetic activity,[27-29] although the level of circulating catecholamines does not increase during hemodilution.[5] On the other hand, activity of nitric oxide could also play an important role in the systemic and local response to hemodilution.[23,30,31]

In conclusion, the different Ht levels at which the μPO_2 of heart, kidney, and intestines became dependent on Ht in the current study demonstrate that the functional effects of systemic and local regulatory mechanisms are different for each of these organs during acute isovolemic hemodilution. The relation between these observations and organ function and damage needs to be determined. Furthermore, our results emphasize that systemic and local regulation of O_2 supply should not be judged by systemic parameters alone, and that a critical level of hemodilution for organs cannot be determined based on the total body O_2 consumption.

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