Subcutaneous Perfusion and Oxygen During Acute Severe Isovolemic Hemodilution in Healthy Volunteers

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Hypothesis: Acute severe isovolemic anemia (to a hemoglobin [Hb] concentration of 50 g/L) does not decrease subcutaneous wound tissue oxygen tension (PsqO2).

Setting: University hospital operating room and inpatient general clinical research center ward.

Subjects: Twenty-five healthy, paid volunteers.

Methods: Subcutaneous oxygen tension and subcutaneous temperature (Tsq) were measured continuously during isovolemic hemodilution to an Hb level of 50 g/L. In 14 volunteers (initially well-perfused), “normal” perfusion (Tsq >34.4°C) was achieved by hydration and systemic warming prior to starting isovolemic hemodilution, while in 11 volunteers (perfusion not controlled [PNC]), no attempt was made to control perfusion prior to hemodilution.

Main Outcome Measures: Measurements of PsqO2, Tsq, and relative subcutaneous blood flow (flow index).

Results: While PsqO2, Tsq, and flow index were significantly lower in PNC vs well-perfused subjects at baseline, there was no significant difference between them at the Hb of 50 g/L (nadir). Subcutaneous P02 did not decrease significantly in either group. Arterial P02 was not different between the groups, and did not change significantly over time; Tsq and flow index increased significantly from baseline to nadir Hb in both groups.

Conclusions: The level of PsqO2 was maintained at baseline levels during hemodilution to Hb 50 g/L in healthy volunteers, whether they were initially well-perfused or mildly underperfused peripherally. Given the significant increase in Tsq and flow index, this resulted from a compensatory increase in subcutaneous blood flow sufficient to maintain oxygen delivery. Wound healing depends to a large extent on tissue oxygen delivery, and these data suggest that even severe anemia by itself would not be sufficient to impair wound healing. Thus, transfusion of autologous packed red blood cells solely to improve healing in surgical patients with no other indication for transfusion is not supported by these results.

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Adequate subcutaneous wound tissue oxygen tension (PsqO2) is vital to resistance to infection, collagen synthesis, angiogenesis, and epithelization in wounds. Surgical patients with PsqO2 less than 40 to 50 mm Hg are at extremely high risk of wound infection and/or wound failure. Because anemia decreases oxygen carrying capacity, transfusions are frequently given to surgical patients “to improve healing,” even when the hemoglobin (Hb) concentration is greater than the standard transfusion trigger (70 g/L in patients without significant cardiovascular or pulmonary disease).

Numerous animal studies have demonstrated, however, that severe anemia, to hematocrit as low as 0.17, does not impair wound healing, as long as hypovolemia does not coexist. This suggests that wound oxygen delivery is maintained even in severe anemia. Subcutaneous P02 depends largely on arterial P02 (PaO2) level and blood flow. Wound capillaries are widely separated (>100 mcm), and therefore, oxygen delivery depends on diffusion in wounds. The compensatory increase in cardiac output, along with the significant decrease in blood viscosity, may allow subcutaneous blood flow and, therefore, PsqO2 levels to remain close to normal in normovolemic anemia. Subcutaneous P02 was not lower in rabbits chronically hemodiluted to a hematocrit of 0.30. PsqO2 has not been measured systematically at lower hematocrits in ani-
SUBJECTS AND METHODS

With institutional review board approval and informed consent, we measured PsqO2 and subcutaneous temperature (Tsq) in 25 paid volunteers during acute, isovolemic hemodilution. All were healthy, without cardiovascular, pulmonary, hepatic, or renal disease, did not smoke, and were taking no medications except oral contraceptives. Positive findings from urine pregnancy test on the morning of the study or positive findings from drug screening were exclusion criteria.

The subject lay in a semisitting position on a standard operating room table with an air mattress overlay for the duration of the study. Throughout the study, subjects breathed 1 L per minute of oxygen via a nasal cannula. Two 14-gauge peripheral venous cannulae and a 20-gauge radial arterial cannula were placed in each subject using local anesthesia. Arterial blood pressure, electrocardiogram reading, and oxygen saturation by pulse oximetry were monitored continuously during the study.

A Luer-hubbed, 15-cm length of silicone tubing (“tonometer,” 1.0-mm outer diameter, 0.8-mm inner diameter; Dow-Corning, Midland, Mich) was placed subcutaneously in the right lateral upper arm using a 19-gauge spinal needle and local anesthesia (Figure 1). The tonometer was used to measure PsqO2 and Tsq continuously, as has been previously described.12,13 Silicone is freely permeable to oxygen, and, after equilibration, the PO2 of saline within it reflects the mean oxygen tension of the surrounding tissue.

A polarographic oxygen electrode (Licox P O2 computer; GMS, Keil-Mielkendorf, Germany) was calibrated in room air (0-point calibration is performed at the factory). It was then inserted into the tonometer via the Luer hub and flushed with deoxygenated isotonic sodium chloride solution via a side port. The probe was allowed to equilibrate for at least 30 minutes until the PsqO2 level changed by no more than 1 mm Hg in 5 minutes.

PsqO2 is exquisitely sensitive to changes in subcutaneous perfusion that usually result from vasoconstriction in response to cold exposure or hypothermia, dehydration, or stress. We expected, based on previous experience, that none of our volunteers would have decreased subcutaneous perfusion (defined as Tsq <34.5°C) at the start of the study.14 Decreased subcutaneous perfusion might be a confounding factor, causing a decrease in level of PsqO2 as Hb decreased, which was in reality unrelated to the change in Hb.15,16 We therefore studied volunteers under 2 conditions: those in whom perfusion was optimized before hemodilution began, and those in whom it was not.

In 14 well-perfused (WP) subjects, subcutaneous perfusion was optimized prior to starting hemodilution by hydration and systemic warming.17,18 A forced-air warmer (Bair Hugger, Augustine Medical Inc, Eden Prairie, Minn) was placed over the subject’s lower body, shielded from the upper arm. The setting of the forced-air warmer was adjusted to keep the subject thermoneutral. Ringer’s lactate solution, at least 1 L and as much as 3 L, was infused until the subject’s Tsq exceeded 34.4°C. Subcutaneous temperature correlates well with subcutaneous perfusion, and in normothermic subjects, a Tsq of at least 34.5°C indicates normal perfusion.

In 11 subjects, no attempt was made to control perfusion prior to the start of hemodilution (perfusion not controlled [PNC]). Infusion of Ringer’s lactate prior to the start of hemodilution was limited to less than 1 L. It was expected, based on previous experience, that none of the volunteers would have a Tsq greater than 34.5°C at the start of hemodilution.

After stable baseline PsqO2 and Tsq levels were established, blood was removed via one of the venous cannulae into collection bags (Citrate-Phosphate-Dextrose-Adenine-1 [CPDA-1]; Baxter Healthcare Corp, Deerfield, Ill) while isovolemia was maintained by intravenous infusion, first by 5% human serum albumin (Baxter Healthcare, Glendale, Calif), and then by the subject’s own platelet-rich plasma (after red blood cells had been separated from the removed blood) in quantities approximately 10% greater than those of the removed blood. All infused fluids were warmed to 37°C (Hotline; Level 1 Technologies Inc, Rockland, Mass). Each CPDA-1 collection bag was filled with 450 mL of whole blood, with volume determined by weight (Sebra, Tucson, Ariz). Removal of each unit of blood required 10 to 20 minutes, with at least 15 minutes allowed to elapse between the start of one unit and the start of the next.

After each unit was removed, PsqO2, Tsq, and volume of blood infused were recorded. Arterial blood gases and Hb were measured after every 2 units of blood were removed. Blood was removed until Hb, measured with a Hemocue device (Hemocue AB, Angelholm, Sweden), was 50 g/L.

Autologous packed red blood cells (PRBC) were then reinfused in the order in which they were removed. Values for PsqO2, Tsq, volume of PRBC infused, and Hb were normal postoperatively in a chronically anemic patient with a hematocrit of 0.17, but decreased significantly on a subsequent day when the hematocrit had decreased to 0.14. A fluid bolus did not increase PsqO2 level, but transfusion of red blood cells did.

We therefore hypothesized that acute severe isovolemic anemia (to Hb concentration 50 g/L) does not decrease subcutaneous wound tissue oxygen tension. We further hypothesized that PsqO2 levels would be maintained by a compensatory increase in subcutaneous blood flow. We chose to study healthy, unanesthetized, euvolemic, euthermic volunteers as the best model to determine the physiological effects of anemia alone.

Figure 1. Schematic diagram of the subcutaneous oxygen tonometer. The oxygen sensor is inserted through the catheter hub. Reprinted with permission from Archives of Surgery.7
measured after reinfusion of the first unit, and then after infusion of every 2 units of PRBC. Each of the first 3 units were reinfused in the study room for a 15-minute period (total time, 45 minutes). Arterial blood gases were obtained after the first and third units were reinfused. Then the arterial cannula and 1 venous cannula were removed. The subcutaneous oxygen and temperature probes were removed from the tonometer. The oxygen probe was placed in room air. If the reading was greater than 10% higher or lower than the original reading (152 mm Hg), the data were discarded.

The subject was next transferred to a research ward in the hospital. The oxygen and temperatures probes were recalibrated and placed in the tonometer, and the system was again flushed with deoxygenated saline. Once a stable baseline was reached, the remainder of the shed blood (as PRBC) was reinfused overnight (1-2 hours per unit) via a fluid warmer. Administration of oxygen at 1 L/min via nasal cannula was continued. Subcutaneous PO2 and Tsq were monitored continuously, and values were recorded after completion of each unit of PRBC infusion. Venous blood was obtained for measurement of Hb values were compared using the t test. After the last unit of PRBC was infused, the oxygen probe was removed from the tonometer and placed in room air. If significant drift (>10%) had occurred, the data were discarded.

Data are presented as means ± SDs unless otherwise indicated. The Shapiro-Wilk test was used determine normality of continuous variables. Data obtained at baseline and nadir Hb levels were compared using the paired t test (normally distributed variables) or Wilcoxon signed-rank test (nonnormal variables) as appropriate. The t test (or Mann-Whitney test if the data were not normal) was used to compare PNC with WP subjects on continuous variables. The 2 groups were compared on categorical variables by the χ² test or by the Fisher exact test.

The relationship between each outcome (PsqO2, Tsq, and flow index) and the percentage of blood units removed was described using a repeated measures linear regression model with an autoregressive correlation matrix. Rather than Hb level, the percent of units removed was chosen as the predictor because wide variability in baseline Hb level would cause undue influence on the regression line. For PsqO2 and Tsq, the models allowed each subject to have their own intercept. Because flow index was highly skewed, we used a log base 2 transformation of flow index for the regression. The final models chosen included the highest order polynomials for percent units removed that were significant (P < .05), along with an indicator for perfusion group and interactions between perfusion group and the polynomials.

Data obtained during reinfusion at nadir Hb and at the Hb value of 100 g/L were compared by paired t test (normally distributed variables) or Wilcoxon signed rank test (nonnormal variables). There were not sufficient data at the Hb values greater than 100 g/L during reinfusion to assess the effect of Hb higher than that level. The effect of the percentage of PRBC units reinfused was described using a repeated measures model as described in the previous paragraph. Blood gases were only obtained during reinfusion of the first 3 units of blood, so flow index was not used as an outcome measure for reinfusion.

The change in subcutaneous blood flow during iso- volumic hemodilution to Hb 50 g/L was assessed by 2 methods. First, Tsq correlates well with subcutaneous blood flow. Therefore, it was hypothesized that Tsq would increase significantly during hemodilution. Subcutaneous T levels at baseline and at nadir Hb values were compared using the t test. Second, simultaneously measured values of PsqO2, Hb, Tsq, and pH were used to estimate subcutaneous blood flow as a fraction of normal (flow index). Using standard equations to calculate oxygen content from PO2, oxygen extraction was calculated from PsqO2 and PsqO2. The PsqO2 measurement approximates subcutaneous oxygen PO2 (which cannot be directly measured as subcutaneous veins are fed by perforators from the muscle) and thus was used to calculate subcutaneous venous oxygen content. Oxygen consumption in wounds is small and nearly constant with changing PO2 and temperature. Oxygen extraction has been measured in euvolemic, euther- mic healthy volunteers (0.73 volume %) to provide a reference value. Therefore, the Fick Principle (flow index = oxygen consumption/oxygen extraction) can be solved as flow index (subject)/flow index (normal) = subcutaneous oxygen extraction (normal)/subcutaneous oxygen extraction (subject). The flow index, a ratio of normal to measured oxygen extraction is therefore defined as follows: 0.73/ (arterial oxygen content − subcutaneous venous oxygen content). “Normal” subcutaneous flow is, by definition, a flow index equal to 1. Based on previous data, the range of flow index in euvolemic, eu- volemic, healthy volunteers is 0.7 to 1.5.

RESULTS

Demographic data are presented in Table 1. Baseline and nadir values for PsqO2, Tsq and flow index are presented in Table 2. PsqO2 did not decrease significantly in either group from baseline Hb to an Hb value of 50 g/L at nadir. In fact, PsqO2 increased in 5 of 14 subjects in the WP group and 6 of 11 subjects in the PNC group. Subcutaneous T and flow index increased significantly from baseline to nadir in both groups. While PsqO2, Tsq, and flow index were significantly lower in PNC vs WP subjects at baseline, there was no significant difference between them at Hb 50 g/L at nadir. Only 1 of the PNC volunteers had a Tsq greater than 34.5°C at baseline. Arterial PO2 was not different between the groups, and did not change significantly over time.

Initial perfusion status and percent units removed were significant predictors of PsqO2 (P = .06 and <.001, respectively) within the cubic mixed-effects model (Figure 2), although there was not a significant interaction between the two. Subjects in the PNC group tended to have lower PsqO2 throughout hemodilution compared with WP subjects. The cubic solution displayed in Figure 2 demonstrates a trend (P = .07) that PsqO2 decreased initially (0%-30% units removed) and then increased again from 40% to 100% of units removed.

Initial perfusion status and percent units removed were significant predictors of Tsq (P < .001 for both) within
the quadratic mixed-effects model, and there was a significant interaction between the 2 ($P = .002$). At the start of hemodilution, PNC subjects had lower $T_{sq}$ than WP subjects. During hemodilution, $T_{sq}$ increased, with PNC subjects reaching nearly the same $T_{sq}$ as WP subjects at nadir Hb. Similarly, initial perfusion status and percent units removed were significant predictors of flow index ($P = .002$ and $P < .001$, respectively) within the linear mixed-effects model, and there was a significant interaction between the 2 ($P < .001$). At the start of hemodilution, PNC subjects had lower flow index than WP subjects. During hemodilution, flow index increased, with the PNC group achieving nearly the same flow index as the WP group at nadir Hb.

During reinfusion, sufficient data for analysis were only obtained in 10 subjects (Table 3). In these subjects, $P_{sqO2}$ increased significantly from nadir values to an Hb of 100 g/L during reinfusion. At the same time, $T_{sq}$ decreased significantly. The percentage of units reinfused, but not initial perfusion status, was a significant predictor of both $P_{sqO2}$ and $T_{sq}$ ($P = .006$ and $P = .04$, respectively) in the mixed-effects model. Therefore, and because $P_{sqO2}$ at the start of reinfusion did not differ between the 2 groups, the data were combined for both groups in the model.

Five subjects complained of nausea during hemodilution, and 5 complained of headache. There were no differences between groups. Most of these complaints were transient, and all had resolved by the next morning. Many volunteers reported fatigue or dizziness at the lowest Hb values. Otherwise, no adverse effects were noted.

Oxygen probe drift was less than 10% in all studies, so no data were discarded. Blood gas samples were not obtained in 3 subjects (1 PNC subject; 2 WP subjects) at the nadir Hb, so flow index was calculated only for the 22 subjects (9 PNC subjects; 13 WP subjects) for whom all data were available.
PsqO₂ did not decrease significantly compared with baseline measurement, even at the nadir Hb value of 50 g/L. In fact, in 11 of 25 subjects, PsqO₂ was higher at the lowest Hb than at baseline. A previous study similarly demonstrated no decrease in systemic oxygen consumption or increase in blood lactate in volunteers made acutely anemic to Hb 50 g/L using the identical protocol, suggesting that such severe anemia can be completely compensated in normal, healthy volunteers at rest. At Hb 50 g/L, however, cognitive function is mildly but reversibly impaired in healthy volunteers. These data suggest, therefore, that wound healing and resistance to infection are not rate limited by anemia until other functions are affected.

This study was designed to evaluate the physiological effects of severe, acute, isovolemic anemia in healthy volunteers at rest. Whether to transfuse is a common clinical dilemma. The accepted “transfusion trigger” for patients without cardiovascular or pulmonary disease is a Hb value of 70 g/L. The aim of the current study was to begin to establish the “critical” value of Hb, thus an Hb value (50 g/L) just below the accepted transfusion trigger was chosen as the end point.

Interpolation of these data to surgical patients requires caution as coexisting disease may impair the compensatory response to anemia. Moreover, during increased metabolic activity, for example getting out of bed or the presence of fever, the increased oxygen demand may exceed the ability of the compensatory responses to deliver oxygen. Thus, most surgical patients may require transfusion to an Hb value greater than 50 g/L. Nonetheless, it is clear that transfusions should not be given if the sole purpose is to improve wound healing as wound tissue oxygen needs are easily met during isovolemic anemia. There are several studies that suggest better wound healing at Hb values between 110 g/L and 120 g/L than at Hb values between 140 g/L and 150 g/L. 

The compensatory responses to anemia are well-described. Cardiac output increases markedly in direct proportion to the degree of anemia. This results from increased heart rate and stroke volume. The increase in stroke volume is partly an active sympathetic response, and partly a passive result of the progressive decrease in blood viscosity. The increase in cardiac output and decrease in blood viscosity would be expected to increase subcutaneous blood flow. The significant increase in Tsq and flow index demonstrates a large increase in subcutaneous blood flow, as predicted. The increase in flow is sufficient to maintain PsqO₂ at normal levels even during severe anemia. Subcutaneous PO₂ initially decreased but then increased back to near-baseline values as hemodilution continued. One possible explanation is that viscosity was not sufficiently decreased to maintain normal PsqO₂ in mild anemia but was decreased enough during severe anemia.

Even in PNC subjects who started with decreased peripheral perfusion, flow increased significantly, and PsqO₂ did not decrease. Although PsqO₂, Tsq, and flow index were lower prior to hemodilution in the PNC than the WP group, and were at levels consistent with a mild degree of hypoperoxidation, at the end of hemodilution, PsqO₂, Tsq, and flow index were not different in the 2 groups.

Blood flow through subcutaneous tissue and skin is almost completely centrally controlled. Heat loss is regulated through thermoregulatory vasoconstriction and vasodilation. The subcutaneous tissue and skin also serve as a reservoir of volume (about 20% in a euvolemic person) to supply the central compartment during hemorrhage or dehydration. Thus, PsqO₂ is extremely sensitive to sympathetically induced vasoconstriction. Hypovolemia, hypothermia, thermoregulatory vasoconstriction, epinephrine infusion, pain, and cigarette smoking have all been shown to decrease PsqO₂ (and Tsq) via this mechanism. Therefore, we hypothesized that mild peripheral vasoconstriction, induced by mild hypovolemia coupled with thermoregulatory vasoconstriction in response to the cold operating room environment, would cause a decrease greater than 15% in PsqO₂, with a blunted increase in Tsq during isovolemic hemodilution. However, the increase in Tsq was significantly greater in PNC subjects than WP subjects. Subcutaneous T was lower in PNC subjects at baseline but converged in the 2 groups at the nadir Hb, when Tsq was near core temperature. Thus, it seems that the infusion of volume at 10% more than the amount of blood removed (to maintain euvolementa) was sufficient to allow compensatory responses to maintain, and in 6 subjects to increase, PsqO₂.

The results of this study suggest that wound healing will not be impaired in WP human subjects during severe anemia, at least to the point of impairment of other tissues. Although we could not directly measure wound healing in this study, the relationship between tissue oxygen and wound healing or resistance to infection is well-documented in surgical patients. There is a direct linear relationship between PsqO₂ and collagen deposition, and an inverse linear relationship between PsqO₂ and surgical wound infection. The critical point at which wound healing and wound immunity are seriously impaired seems to be 40 to 50 mm Hg. Mean PsqO₂ at nadir Hb was well above this range. Below 40 mm Hg, a decrease in PsqO₂ of 10 mm Hg is associated with an 80% increase in the infection rate.

We did not investigate the response to hemodilution in more severely vasoconstricted subjects, so it is not clear at what point the compensatory responses become inadequate. Moreover, the interaction of anemia with sympathetically induced vasoconstriction in surgical patients cannot be interpolated from these data obtained in healthy volunteers.

In healthy, euvolemic, euthermic volunteers in the absence of anemia, PsqO₂ increases linearly as PaO₂ increases (from 50-65 mm Hg breathing room air to 100-130 mm Hg while breathing 50% oxygen using a simple face mask). This is because subcutaneous oxygen delivery depends on diffusion across a long intercapillary distance. Therefore, the oxygen carrying capacity of Hb contributes a relatively minor fraction of subcutaneous tissue oxygen. Arterial PO₂ and Tsq are thus the main determinants of PsqO₂. The large increase in subcutaneous flow in our subjects during hemodilution suggests that increasing inspired PO₂ would have a larger than usual effect at low Hb levels. The subjects breathed oxygen at...
1 L per minute during the study. Thus, PsqO2 may have been maintained in part by a disproportionate effect of increased PaO2 at a lower Hb level. The effect of higher inspired concentrations of oxygen remains to be investigated but may represent a successful avenue for improving healing in anemic patients.

During reinfusion of PRBC, PsqO2 increased. Simultaneously, Tsq decreased, indicating that some of the increase was mediated through increased oxygen carriage by Hb. However, PsqO2 increased above the original baseline value, which suggests at least one more contributing factor. One likely possibility is a temporary increase in intravascular volume. Hypervolemia not associated with peripheral edema has been shown to increase PsqO2. Although central volume was not measured in this study, in a previous study of identical design, central venous pressure and pulmonary capillary wedge pressure remained in the reference range throughout the study. Thus it is reasonable to assume normovolemia at the start of reinfusion of PRBC in this study. Each transfused unit of PRBC equals approximately 250 mL. Therefore, the subjects received an obligate fluid bolus with each unit transfused.

No animal model or patient population is available in which the effect of profound anemia can be studied as an isolated variable. These data are critical, however, to the development of evidence-based transfusion guidelines for patients. Therefore, we chose to study unanesthetized, healthy volunteers under carefully controlled conditions. Recognizing that the volunteers would gain no direct benefit from the study, we designed the protocol to minimize the risk to the volunteers. The protocol was reviewed and approved by the Committee on Human Research at the University of California, San Francisco, with a yearly rereview. The hemodilution procedure was performed in an operating room so that subjects were continuously monitored, and all appropriate resuscitation facilities were immediately available. A board-certified anesthesiologist was present in the room at all times. Reinfusion of blood was performed by registered nurses according to protocol in a standardly equipped hospital ward. We have studied more than 50 volunteers to date using the same hemodilution protocol with no serious adverse effects.

Colloid was chosen as the replacement fluid to ensure normal intravascular volume while minimizing peripheral edema. To the extent possible, autologous plasma was used for hemodilution. Albumin (5%) was chosen to provide the balance of colloid infused as the safest non-autologous colloid product. The risk of disease transmission via albumin infusion is essentially zero. Nonetheless, as part of the consent process, volunteers were informed of the use of human blood products in the manufacture of albumin, and thus the theoretical risk of disease transmission.

The uneven distribution of men and women in the 2 groups is unlikely to have affected the results, since PsqO2 does not differ between men and women. Moreover, when sex was added to the repeated measures regression model, it was not a significant predictor of PsqO2, Tsq, or flow index. Height and weight were marginally greater in the PNC group, likely because of the predominance of men in that group. The difference was less than might be expected because, after the first few volunteers, we limited enrollment to volunteers who weighed less than 80 kg to limit the duration of hemodilution (number of units removed). Baseline Hb values were significantly lower in the WP group, probably related to the greater number of women in that group. Subjects in the WP group received significantly more intravenous crystalloid prior to hemodilution, and this may also have contributed to the lower starting Hb value.

Subcutaneous PO2 was maintained at baseline levels during isovolemic hemodilution to Hb 50 g/L in healthy volunteers, whether they were initially well-perfused or mildly underperfused peripherally. Based on a significant increase in Tsq and flow index, this resulted from a compensatory increase in subcutaneous blood flow sufficient to maintain oxygen delivery. Previous animal studies have demonstrated no decrement in wound healing or resistance to infection during severe anemia (hematocrit level, 0.17) as long as normovolemia is maintained. The likely mechanism for this result is that PsqO2 does not decrease during acute, severe, isovolemic hemodilution.

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