

Acute Severe Isovolemic Anemia Impairs Cognitive Function and Memory in Humans

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Background: Erythrocytes are transfused to prevent or treat inadequate oxygen delivery resulting from insufficient hemoglobin concentration. Previous studies failed to find evidence of inadequate systemic oxygen delivery at a hemoglobin concentration of 5 g/dl. However, in those studies, sensitive, specific measures of critical organ function were not used. This study tested the hypothesis that acute severe decreases of hemoglobin concentration alters human cognitive function.

Methods: Nine healthy volunteers, age 29 ± 5 yr (mean \pm SD), were tested with verbal memory and standard, computerized neuropsychologic tests before and after acute isovolemic reduction of their hemoglobin to 7, 6, and 5 g/dl and again after transfusion of their autologous erythrocytes to return their hemoglobin concentration to 7 g/dl. To control for duration of the experiment, each volunteer also completed the same tests on a separate day, without alteration of hemoglobin, at times of the day approximately equivalent to those on the experimental day.

Results: No test showed any change in reaction time or error rate at hemoglobin concentration of 7 g/dl compared with the

data at the baseline hemoglobin concentration of 14 g/dl. Reaction time, but not error rate, for horizontal addition and digit-symbol substitution test (DSST) increased at hemoglobin 6 g/dl (mean horizontal addition, 19%; 95% confidence interval [CI], 4–34%; mean DSST, 10%; 95% CI, 4–17%) and further at 5 g/dl (mean horizontal addition, 43%; 95% CI, 6–79%; mean DSST, 18%; 95% CI, 4–31%). Immediate and delayed memory was degraded at hemoglobin 5 g/dl but not at 6 g/dl. Return of hemoglobin to 7 g/dl returned all tests to baseline, except for the DSST, which significantly improved, and returned to baseline the following morning after transfusion of all autologous erythrocytes.

Conclusion: Acute reduction of hemoglobin concentration to 7 g/dl does not produce detectable changes in human cognitive function. Further reduction of hemoglobin level to 6 and 5 g/dl produces subtle, reversible increases in reaction time and impaired immediate and delayed memory. These are the first prospective data to demonstrate subtle degraded human function with acute anemia of hemoglobin concentrations of 6 and 5 g/dl. This reversibility of these decrements with erythrocyte transfusion suggests that our model can be used to test the efficacy of erythrocytes, oxygen therapeutics, or other treatments for acute anemia. (Key words: Brain function; erythrocytes; hemodilution; transfusion.)

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THE decision to transfuse erythrocytes should be made on the basis of evaluation of the risks and potential benefits. In the past two decades we have substantially increased our knowledge and quantified and decreased the risk of transfusion-transmitted known infectious vectors.¹ However, delineation of the specific indications for erythrocyte transfusion has remained elusive.² Consequently, more than 15 "practice parameters" have been published by various organizations in an effort to guide the clinician.³⁻⁵ However, there are few human data on which these recommendations are based. Inadequate oxygen delivery can lead to tissue, organ, or systemic hypoxia and acidosis that may be detected as biochemical, electrical, or functional abnormalities. We have previously demonstrated that cardiovascular compensation for severe acute isovolemic anemia to a hemoglobin concentration of 5 g/dl is adequate, and that this hemoglobin concentration does not produce evidence of inadequate systemic or myocardial oxygen delivery in

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healthy, unmedicated humans.⁶ Other clinical data similarly have not defined the hemoglobin concentration requiring transfusion. After surgical repair of hip fracture, a hemoglobin concentration of 9–10 g/dl is not associated with different lower-extremity function or mortality than is a hemoglobin concentration of 11 g/dl.⁷ A hemoglobin concentration of 8.5 g/dl does not increase mortality or organ dysfunction scores in critically ill patients compared with a hemoglobin concentration of 10.5 g/dl,⁸ and 5 days after coronary artery bypass surgery there is no relationship between maximal duration of exercise and hemoglobin concentration (range, 8–12 g/dl).⁹ Nevertheless, fatigue is associated with acute anemia,¹⁰ and patients are sometimes transfused in the perioperative period to improve their subjective feeling of well-being.

Neuronal function is sensitive to hypoxia, but the degree of acute anemia required to impair human cerebral function is not known. In our previous studies,^{6,11} it seemed to the investigators that the subjects were noticeably slower to respond to questions when they were severely anemic in comparison to their baseline state. Therefore, we thought it appropriate to assess human cerebral function during states of decreased oxygen-carrying capacity. We tested the null hypothesis that decreasing blood hemoglobin concentration acutely to 5 g/dl would not affect sensitive measures of human cognitive function.

Methods

With approval of our institutional review board and informed consent, we studied nine paid volunteers who were without cardiovascular, pulmonary, or hepatic disease, did not smoke, and were not taking any medications. A minimum of 80% correct responses for each cognitive test (see below) was required for participation in the study. Eight of these volunteers participated in an investigation regarding fatigue during acute severe anemia.¹⁰

Two peripheral venous cannulas were inserted in each subject using local anesthesia. After insertion of the cannulas, subjects rested for 30 min before measurement of variables. The neurobehavioral and memory tests (see below) were performed with the subject in a semisitting position and the hand-held controller in the subject's lap, before removal of any blood, and 10–15 min after producing isovolemic anemia to blood hemoglobin concentrations of 7, 6, and 5 g/dl by removal of

450 ml blood into CPDA-1 collection bags (Baxter Healthcare Corp., Deerfield, IL). Removal of each 450 ml blood required approximately 10–15 min. Simultaneous with blood withdrawal, 5% human serum albumin (Baxter Healthcare, Glendale, CA) and the subject's own platelet-rich plasma (after separation from the erythrocytes of the removed blood) were infused intravenously in quantities $14\% \pm 12\%$ (mean \pm SD) greater than that of the removed blood to maintain isovolemia.⁶ After completion of the tests at a hemoglobin concentration of 5 g/dl, a sufficient quantity of each volunteer's erythrocytes was transfused to return blood hemoglobin concentration to 7 g/dl, and the neurobehavioral and memory tests were repeated. The volunteers remained in the hospital overnight while all remaining erythrocytes were transfused. The neurobehavioral and memory tests were repeated the following morning.

Each volunteer was studied twice. On a different day, separated by at least 1 week from the experimental day, a "control" study was conducted, consisting of the same procedures, including placement of intravenous cannulas, except that blood was not withdrawn. Tests on the control day were performed at times similar to when they were performed during hemodilution studies. The subjects were not tested on the morning after the control day.

Cognitive Tests

Speed and accuracy of information processing and recent verbal memory were assessed at each time point. Speed of information processing was assessed with three reaction time tasks, horizontal addition, symbol-digit substitution test (DSST), and switching attention, selected from the NES-2 battery (NES2, v 4.6; Neurobehavioral Systems Inc., Winchester, MA). All of the NES-2 tasks were presented with a computer and a 14-inch monitor positioned approximately 75 cm from the patient. Subjects responded using a keyboard placed in their laps. For each reaction time task, subjects were asked to respond as quickly as they could without making mistakes. All three reaction time tasks were administered three times on each of two occasions before the test day to familiarize subjects with the procedures and minimize postbaseline increments in performance caused by practice effects. Subjects showed no further learning after four trials of any test. The horizontal addition task consists of a horizontal row of three single-digit numbers that the subject was required to add and type the answer. The range of digits presented was restricted such that their sum was ≥ 11 . Each test consisted of 36

trials with an intertrial interval of 50 ms. Tests remained on the screen until the subject responded. In the DSST, subjects were shown nine symbol-digit pairs at the top of the screen. A test set of the nine symbols was presented in the center of the screen in a scrambled order. Subjects were required to press the digits on the keyboard corresponding to the symbol in the test set. There was one practice set and five test sets of symbol-digit pairs. The switching attention task consisted of three different testing conditions. In the first condition, subjects were shown a large rectangle that was either on the left or the right side of the screen. Subjects indicated which side the rectangle was presented by pressing the corresponding key on the keyboard. In the second condition, subjects were shown a large arrow pointing to either the left or the right side of the screen and were required to indicate the direction of the arrow by pressing the corresponding key on the keyboard. In the third condition, a prompt consisting of either the word "side" or "direction" appeared on the screen before the stimulus. The stimulus was an arrow pointing either to the left or to the right, presented on either the left or the right side of the screen. The subject was required to respond to the stimulus on the basis of the prompt presented immediately before the trial (e.g., for the prompt "side" and a stimulus arrow on the left side of the screen pointing to the right, the correct response would be "left").

Memory was evaluated using immediate and delayed free recall of a 15-item word list modeled after the Auditory Verbal Learning Test.¹² For the present study, six alternate forms were used, one for each testing session. We used published lists¹³ that have good alternate-form reliability.¹³ The order of the lists was randomized. In each testing session, the list was read to the subject once, and the subject was asked immediately to recall as many of the words as possible. Ten minutes after the initial learning trial, subjects were again asked to recall as many of the words as possible without having heard the list again. The dependent variable for the immediate and delayed recall trials was the number of words not recalled.

Data Analysis and Statistics

Data are presented as mean \pm SD or 95% confidence interval. The Shapiro-Wilk test¹⁴ was used to test normality of continuous variables. Each cognitive test was analyzed separately. Differences between data at each hemoglobin value and the data at the baseline hemoglobin were compared between the test day and control day by

Table 1. Test Values at Initial Hemoglobin Concentration of 14 g/dl

Variable	Mean	95% CI
Horizontal addition (s)	2.811	2.405–3.218
DSST (s)	1.919	1.755–2.083
Immediate memory (% wrong)	45.6	35.6–55.5
Delayed memory (% wrong)	54.1	41.7–66.5

DSST = digit-symbol substitution test.

Wilcoxon signed rank tests because data for many variables were not normally distributed. Data from the morning after the study day were compared with baseline data by Wilcoxon signed rank tests. Statistical significance was accepted at $P \leq 0.05$.

To confirm each of the above statistical tests, we used repeated measures models that provide overall tests of main effects and interactions. For analysis of reaction times from each cognitive test, we fit a linear model for repeated measures,¹⁵ with a random person effect to account for the within-subject correlation. The model was fit using the natural log of the reaction times to make them more closely fit a normal distribution. For analysis of errors for each cognitive test, we used a logistic regression model for repeated measures¹⁶ with a random person effect. The fixed effects for both types of models were study type (hemodilution *vs.* control), condition (baseline, stages of reduction of hemoglobin concentration and return of erythrocytes, and next day), and an interaction between study type and condition. For this analysis, there were too few errors on the DSST and switching attention (side condition) test to permit statistical analysis.

Results

The volunteers were aged 29 ± 5 yr (mean \pm SD), were 1.67 ± 0.09 m tall, and weighed 65.4 ± 9.6 kg. There were three women and six men. Hemoglobin concentration before hemodilution was 14.0 ± 1.3 g/dl (men, 14.5 ± 1.0 g/dl; women, 12.9 ± 1.2 g/dl). Subjects were tested after hemodilution reduced the hemoglobin concentration to 7.2 ± 0.2 , 6.0 ± 0.2 , and 5.1 ± 0.2 g/dl. Subjects were tested again after transfusion of autologous erythrocytes increased the hemoglobin concentration to 7.2 ± 0.2 g/dl.

No test showed any change in reaction time or error rate at a hemoglobin concentration of 7 g/dl compared with the data at the baseline hemoglobin concentration of 14 g/dl (table 1). Further reduction of hemoglobin

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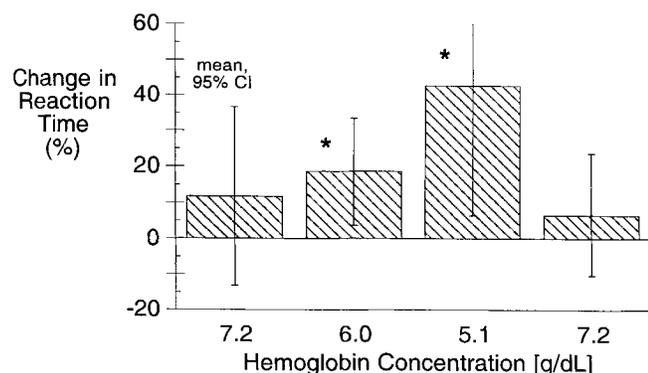


Fig. 1. Reaction time for horizontal addition increased at hemoglobin concentrations of 6 and 5 g/dl but not at 7 g/dl, compared with 14 g/dl in nine healthy subjects. Data are mean \pm 95% confidence intervals. * $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the indicated hemoglobin concentration and the value at the baseline hemoglobin concentration of 14 g/dl.

concentration to 6 g/dl resulted in increasing reaction times ($P < 0.05$), but not error rate, for horizontal addition (fig. 1) and DSST (fig. 2). The switching attention tests were not affected by changes in hemoglobin concentration. Neither immediate nor delayed memory at hemoglobin concentrations of 7 or 6 g/dl differed from memory at the baseline hemoglobin concentration ($P > 0.05$). Reduction of hemoglobin concentration to 5 g/dl resulted in further increases in reaction times for horizontal addition and DSST ($P < 0.05$) but did not change the reaction time of the switching attention tests ($P > 0.05$). Error rates continued to be unchanged at

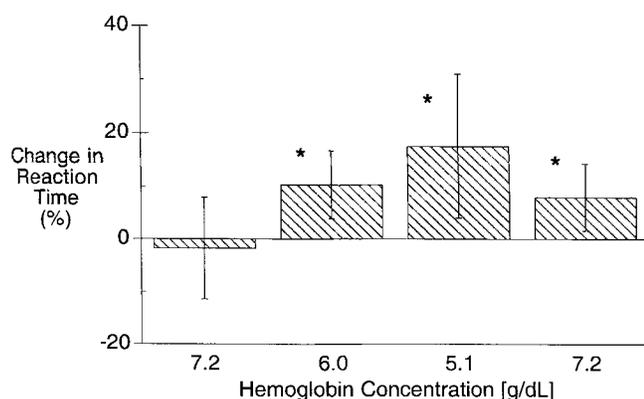


Fig. 2. Reaction time for digit-symbol substitution increased at hemoglobin concentrations of 6 and 5 g/dl but not at 7 g/dl, compared with 14 g/dl in nine healthy subjects. Data are mean \pm 95% confidence interval. * $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the indicated hemoglobin concentration and the value at the baseline hemoglobin concentration of 14 g/dl.

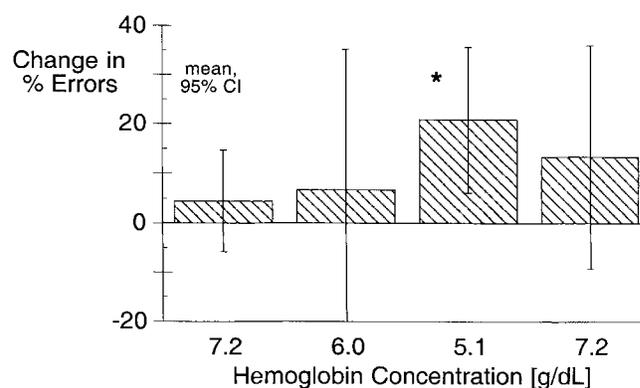


Fig. 3. Immediate memory is impaired at a hemoglobin concentration of 5 g/dl but not 6 or 7 g/dl compared with a hemoglobin concentration of 14 g/dl in nine healthy subjects. Data are mean \pm 95% confidence interval. * $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the indicated hemoglobin concentration and the value at the baseline hemoglobin concentration of 14 g/dl.

hemoglobin 5 g/dl for all tests ($P > 0.05$). Both immediate (fig. 3) and delayed (fig. 4) memory were impaired at a hemoglobin concentration of 5 g/dl ($P < 0.05$). Return of hemoglobin concentration to 7 g/dl returned all tests to baseline ($P > 0.05$), except for DSST reaction time, which improved ($P < 0.05$) but continued to differ from the baseline result ($P < 0.05$). The following morning, after all erythrocytes had been returned to the subjects, the DSST reaction times did not differ from the time at baseline ($P > 0.05$). The repeated-measures models confirmed the above statistical analyses.

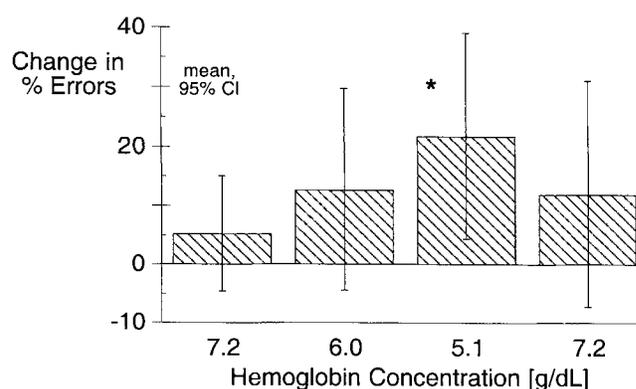


Fig. 4. Delayed memory is impaired at a hemoglobin concentration of 5 g/dl but not 6 or 7 g/dl, compared with a hemoglobin concentration of 14 g/dl in nine healthy subjects. Data are mean \pm 95% confidence interval. * $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the indicated hemoglobin concentration and the value at the baseline hemoglobin concentration of 14 g/dl.

Discussion

We have found that acute isovolemic anemia to a hemoglobin concentration of ≤ 6 g/dl results in mild, reversible decrements in reaction time, and that a hemoglobin concentration of 5 g/dl reversibly impairs immediate and delayed memory. While maintaining high levels of accuracy, subjects exhibited slower reaction at hemoglobin concentration of ≤ 6 g/dl and performed less well on measures of immediate and delayed recall at a hemoglobin concentration of 5 g/dl.

The changes in human cognition after acute isovolemic anemia are similar to those found in subjects experiencing hypobaric hypoxia. Performance of the DSST has been found to decline with decreased barometric pressure at altitude^{17,18} and in a hypobaric chamber.¹⁹ Decreased efficiency of memory, reaction time, and concentration has been found in high-altitude mountaineers.²⁰ Climbers perform more slowly on most tasks relative to a control group and have impaired learning and retention,^{17,21} although impaired memory at altitude has not been a universal finding.²² Similar decrements in information processing speed have been found at simulated high altitudes in hypobaric chambers.^{23,24}

The processing tasks used in the present study are complex and do not necessarily implicate any specific aspect of cognitive functioning. Performance on reaction time tasks involves perceptual speed, central information processing and problem-solving facility, and a motor response. Although some studies have implicated visual and perceptual speed as playing an important role in the disruption of reaction time after hypoxia,^{25,26} impairment in central information processing resources is also probable. For example, it is unlikely that visual and perceptual speed or motor speed contributed to our subjects' decline in verbal memory because visual processing and motor speed were not required for the task. In addition, studies of hypoxia have demonstrated reduced electroencephalographically recorded evoked potential amplitudes,^{24,27} which implicate central information processing capacity.

Our data contrast with our previous findings of absence of biological markers of inadequate systemic oxygen delivery at these same hemoglobin concentrations of 6 and 5 g/dl.^{6,11} The markers used in the previous studies, total body oxygen consumption and blood lactate concentration, detect inadequate systemic oxygen delivery but may not be sufficiently sensitive to detect individual organ or regional inadequate oxygenation. Measurement of total-body oxygen consumption would be

expected to have an inherent variation of estimation of approximately 10% based on the potential error of estimation of cardiac output. Decreases of oxygen consumption at the threshold of inadequate oxygen supply for a small region of tissue, or even for an entire organ, might not be sufficiently large to be detected by estimation of total-body oxygen consumption. Similarly, small regional increases in lactate production might escape detection when measuring systemic (arterial or mixed venous) blood lactate concentrations.

Our findings suggest that at hemoglobin concentrations of 6 and 5 g/dl, human cognitive function is impaired subtly. We are not aware of other comparable studies in conscious humans. In anesthetized monkeys during 60 min of acute isovolemic anemia to hematocrit 10–16%, the amplitude of somatosensory evoked potentials is decreased, but the latency is not increased.²⁸ The somatosensory evoked potentials recovered with restoration of hematocrit, and there were no neurologic or neuropathologic sequelae.²⁸ In anesthetized dogs, myocardial oxygen supply becomes inadequate at the same hemoglobin concentration that produces inadequate total-body oxygenation.²⁹ Similarly, in anesthetized dogs, hepatic metabolic function, as assessed by clearance of blood lactate, does not decrease until there is evidence of inadequate systemic oxygen delivery.³⁰

We studied relatively few subjects. We had originally planned to study a greater number; however, when it became apparent that we would have positive findings, we were constrained not to continue the studies. The small, statistically and clinically insignificant changes at a hemoglobin concentration of 7 g/dl would likely require (by power analysis) study of an additional 80–375 subjects. It is possible that our tests were not sufficiently sensitive to detect changes at a hemoglobin concentration of 7 g/dl. We think this unlikely, because reaction time tasks have been shown to be sensitive to very subtle problems that are not readily revealed by standard neuropsychological tests³¹ and to cognitive deficits in patients whose standard clinical assessments have been normal.³² One additional aspect of the study merits discussion. Our volunteers were not blinded with regard to whether a given day was experimental or control. We had carefully considered this issue before the initiation of the study but determined that blinding would not achieve its desired effect. Subjects can easily determine whether fluids are being infused intravenously, and the subjective feelings associated with the severe anemia are readily distinguished from the nonanemic state.¹⁰

Some have suggested that many patients may be un-

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dertransfused, despite lack of supporting evidence.^{33,34} Criteria for "undertransfusion" have been difficult to define. Our data now provide the initial evidence of specific organ dysfunction in healthy humans resulting from acute anemia, at levels previously thought not to produce physiologic impairment. Decisions to transfuse should be based on a balance of benefits and risks. The cognitive decrements we observed were subtle and reversible. However, our volunteers were severely anemic for a relatively brief period. We do not know whether a more protracted period of severe anemia would have resulted in more severe or less transient impairment. Sojourners at very high altitudes have had neuropsychological impairment that persisted for months after their return to sea level.^{20,35-37} However, protracted reduction of arterial oxygen partial pressure (P_{aO_2}) such as occurs with reduced barometric pressure may not apply to acute reductions of hemoglobin concentration. Reduction of P_{aO_2} impairs tissue diffusion of oxygen. However, in anesthetized dogs, inadequate systemic oxygen delivery is reached by reduction of hemoglobin concentration or reduction of P_{aO_2} at equivalent values.^{38,39} Cerebral blood flow increases with the decreased P_{aO_2} that occurs at altitude.⁴⁰ However, hypoxia also increases ventilation, which reduces arterial carbon dioxide partial pressure (P_{aCO_2}). The increase in cerebral blood flow that occurs with hypoxia is less when P_{aCO_2} is reduced than when normocapnia is maintained.⁴¹ Furthermore, although cerebral blood flow increases during initial exposure to altitude, it returns to values similar to those at sea level within 3-5 days of exposure to altitude.⁴⁰ These factors may serve to produce a more substantial effect on cerebral function than does acute anemia. The reduction of cerebral blood flow by hyperventilation has been thought to be the possible cause of the residual neurobehavioral impairment after return to sea level after sojourn to high altitude.³⁵ In our previous studies of similar volunteers made acutely anemic to hemoglobin concentrations of 6 and 5 g/dl, P_{aCO_2} remained normal.^{6,11} Documented¹ and expected improvements (by gene amplification donor testing techniques)⁴² in the safety of blood transfusion, taken together with our data, suggest that the balance of risks of transfusion *versus* nontransfusion of erythrocytes may have shifted. Our data in this and our earlier reports^{6,11} support previous recommendations that a hemoglobin concentration of 7 g/dl is adequate in healthy humans.^{3,5} However, the data we report here are the first to suggest that hemoglobin concentrations of ≤ 6 g/dl may produce subtle impairment of human function. The revers-

ibility of these decrements with erythrocyte transfusion suggests that our model can be used to test for efficacy of erythrocytes, oxygen therapeutics (e.g., hemoglobin solutions or perfluorochemicals), or other proposed treatments for acute anemia.

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