

Oxygen Reverses Deficits of Cognitive Function and Memory and Increased Heart Rate Induced by Acute Severe Isovolemic Anemia

Richard B. Weiskopf, M.D.,* John Feiner, M.D.,† Harriet W. Hopf, M.D.,‡ Maureen K. Viele, M.D.,§ Jessica J. Watson, M.A.,|| Joel H. Kramer, Psy.D.,# Rachel Ho, B.S.,** Pearl Toy, M.D.††

Background: Erythrocytes are transfused to improve oxygen delivery and prevent or treat inadequate oxygenation of tissues. Acute isovolemic anemia subtly slows human data processing and degrades memory, increases heart rate, and decreases self-assessed energy level. Erythrocyte transfusion is efficacious in reversing these effects of acute anemia. We tested the hypothesis that increasing arterial oxygen pressure (P_{aO_2}) to 350 mmHg or greater would supply sufficient oxygen to be equivalent to augmenting hemoglobin concentration by 2-3 g/dl and thus reverse the effects of acute anemia.

Methods: Thirty-one healthy volunteers, aged 28 ± 4 yr (mean \pm SD), were tested with verbal memory and standard, computerized neuropsychologic tests before and twice after acute isovolemic reduction of their hemoglobin concentration to 5.7 ± 0.3 g/dl. Two sets of tests were performed in randomized order at the lower hemoglobin concentration: with the volunteer breathing room air or oxygen. The subject and those administering the tests and recording the results were unaware which gas was administered. As an additional control for duration of the experiment, 10 of these volunteers also completed the same tests on a separate day, without alteration of hemoglobin concentration, at times of the day similar to those on the experimental day. Heart rate, mean arterial blood pressure, and self-assessed sense of energy were recorded at the time of each test.

Results: Reaction time for digit-symbol substitution test increased, delayed memory was degraded, mean arterial pressure and energy level decreased, and heart rate increased at a hemoglobin concentration of 5.7 g/dl (all $P < 0.05$). Increasing P_{aO_2} to 406 ± 47 mmHg reversed the digit-symbol substitution test result and the delayed memory changes to values not different from those at the baseline hemoglobin concentration of 12.7 ± 1.0 g/dl, and decreased heart rate ($P < 0.05$). However, mean arterial pressure and energy level changes were not altered with increased P_{aO_2} during acute anemia.

Conclusion: The authors confirmed that acute isovolemic anemia subtly slows human reaction time, degrades memory, in-

creases heart rate, and decreases energy level. The findings of this study support the hypothesis that increasing P_{aO_2} to 350 mmHg or greater by breathing oxygen reverses all of these effects of acute anemia except for decreased energy.

ERYTHROCYTES are transfused to improve oxygen delivery and thus prevent imminent development of or treat inadequate oxygenation of tissues. The value of critical oxygen delivery varies among species.¹⁻³ Few data in humans have demonstrated the hemoglobin concentration or oxygen delivery that is inadequate to meet oxygen demand. Van Woerkens *et al.*⁴ found the critical oxygen delivery in an anesthetized 84-yr-old man to be $4.9 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which occurred at a hemoglobin concentration of 4 g/dl. We were unable to detect systemic evidence of inadequate oxygen delivery in 32 unmedicated healthy people when their hemoglobin concentration was acutely (while maintaining isovolemia) decreased to 5 g/dl, with an oxygen delivery of $10.7 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.⁵ Further reduction of oxygen delivery to $7.3 \text{ ml O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in a subset of eight of these unmedicated people also did not produce systemic evidence of inadequate oxygen delivery.⁶

However, absence of systemic evidence of inadequate oxygen delivery does not necessarily fully assess oxygenation of specific organs or tissues. Decreased oxygen consumption or increased lactate production of individual tissues or organs may be too small to be detected by analyses of systemic measures. We hypothesized that central nervous system function might degrade at hemoglobin concentrations higher than that associated with systemic critical oxygen delivery. Consequently, more recently we examined the effects of acute isovolemic anemia on cognitive function and memory and found no changes at a hemoglobin concentration of 7 g/dl and subtle deficits at hemoglobin concentrations of 6 and 5 g/dl that were reversible with erythrocyte transfusion.⁷ At these hemoglobin concentrations in unmedicated humans, cardiac output increases, but not sufficiently to completely compensate for the decreased arterial oxygen content.⁵ We hypothesized that having the subject breathe oxygen would increase oxygen content at these low hemoglobin concentrations by an amount approximately equivalent to increasing the hemoglobin concentration by 2-3 g/dl, and thus sufficiently compensate for the acute anemia to reverse the previously observed deficits.

* Professor, Departments of Anesthesia and Physiology, and Investigator, Cardiovascular Research Institute. † Associate Professor, Department of Anesthesia. ‡ Associate Professor, Departments of Anesthesia and Surgery. § Associate Professor, ** Research Associate, †† Professor, Department of Laboratory Medicine. || Senior Statistician, Department of Laboratory Medicine; current position: Biostatistician, PPD Development, Morrisville, North Carolina. # Associate Clinical Professor, Department of Psychiatry.

Received from the Departments of Anesthesia, Physiology, Laboratory Medicine, Psychiatry, Surgery, and The Cardiovascular Research Institute, University of California, San Francisco, California. Submitted for publication April 5, 2001. Accepted for publication December 6, 2001. Supported in part by grant No. 1 P50 HL54476 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland. These studies were conducted in part in the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by grant No. 5 MO1 RR-00079 from the National Center for Research Resources, National Institutes of Health, Bethesda, Maryland.

Address reprint requests to Dr. Weiskopf: Department of Anesthesia, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California 94143-0648. Address electronic mail to: weiskopf@anesthesia.ucsf.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

Methods

After obtaining approval of the institutional review board at the University of California (San Francisco, CA) and informed consent, we studied 31 paid volunteers who were without cardiovascular, pulmonary, or hepatic disease, did not smoke, were not taking any medications, and weighed less than 80 kg. The weight requirement was imposed to avoid excessively long experimental days, with potentially increased effects of time, owing to the need to remove large quantities of blood to achieve the desired hemoglobin concentration. A minimum of 80% correct responses for each of the nonverbal cognitive tests (see Cognitive Tests) was required for participation in the study.

To test our hypothesis that breathing oxygen would improve the deficits of acute anemia, we produced acute severe isovolemic anemia in 31 volunteers. A radial arterial and 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 before removal of any blood and twice after producing isovolemic anemia to a blood hemoglobin concentration of 5.5–6.0 g/dl by removal of 450 ml blood into CPDA-1 collections 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 $17 \pm 8\%$ (mean \pm SD) greater than that of the removed blood to maintain isovolemia.⁵ For all test periods, each subject was fitted with a breathing mask through which either room air or oxygen was supplied at a flow rate of 15 l/min. Tests at the baseline hemoglobin concentration were conducted with the volunteer breathing room air. Two tests were performed at the nadir hemoglobin concentration of 5.5–6.0 g/dl, one with the volunteer breathing room air, the other with the volunteer breathing oxygen. The order of the tests was randomly allocated, and the subject and those administering the tests and recording the results were unaware which gas was administered. A 5-min equilibration period was allowed while the subject breathed the test gas before the cognitive tests were performed. Arterial blood gases and pH and blood pressure were measured at each test period. Each subject used a 10-cm visual analog scale to assess their energy level at each time point. After conclusion of the tests, all withdrawn erythrocytes were returned to each volunteer during the succeeding 12 h.

To verify the cognitive function results previously reported by enabling direct comparison of the results of

this study with our previous findings, 10 of the 31 volunteers were also studied on a separate second day, separated by at least 1 week from the study day. These volunteers were chosen based on logistic considerations: compatibility of their schedule with those of the research team. This "control" day was sometimes before and sometimes after the hemodilution day. On this "control" day, the procedures were identical to those on the study day, except that an arterial cannula was not inserted, and acute anemia was not produced. Intravenous cannulas were inserted, and tests were performed at times equivalent to those performed on the study day when acute anemia was produced. Blood pressure on the "control" day was measured by oscillometry (A/S3; Datex, Helsinki, Finland).

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 two tests selected from the NES-2 battery (NES2, v 4.6; Neurobehavioral Systems Inc., Winchester, MA): a horizontal addition test and the digit-symbol substitution test (DSST). These tests were presented with a computer and a 14-inch monitor positioned approximately 75 cm from the subject. 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. These tests were administered twice each on each day of testing, before insertion of intravenous cannulas, and twice before the first test day to familiarize subjects with the procedures and minimize postbaseline increments in performance caused by practice effects. These computerized tests have been described previously.⁷ 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 or more. 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 were one practice set and five test sets of symbol-digit pairs.

Memory was evaluated as described previously,⁷ using immediate and delayed free recall of a 15-item word list modeled after the Auditory Verbal Learning Test.⁸ We used published lists that have good alternate-form reliability.⁸ The order of the lists was randomized. Each list was not used more than once for each subject. 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 learn-

ing 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

The number of volunteers to be studied was determined *a priori* by a power analysis, using data for the DSST from our previous study,⁷ an estimate of the potential effect of breathing oxygen, with a two-sided $\alpha = 0.05$ and a power of 80% to detect a 20% increase in reaction time and a 10% increase in words not recalled (memory test).

Data are presented as mean \pm SD. Each cognitive test was analyzed separately. Reaction time for a testing session was measured as the median of all correct reaction times (for the horizontal addition test) or of all reaction times (for the DSST). Errors were measured as the percent of trials that were incorrect. The Shapiro-Wilk test was used to test for normal distribution of the results.⁹ Paired comparisons were performed within-day for baseline, 5–6 g/dl hemoglobin breathing room air, and 5–6 g/dl hemoglobin breathing oxygen; and between study and control days by the Student paired *t* test; or if the data were not normally distributed, by Wilcoxon signed-rank test. The effect of order of breathing of oxygen or room air at 5.7 g/dl hemoglobin was tested by the Mann-Whitney test. Statistical significance was accepted at $P \leq 0.05$ for all tests.

To confirm each of the aforementioned 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 using SAS Proc Mixed (SAS version 8, 1999; SAS Institute, Cary, NC) with a random person effect to account for the within-subject correlation. The model was fit using the natural logarithm of the reaction times to make them more closely fit a normal distribution. For analysis of errors from each cognitive test, we used a logistic regression model for repeated measures with a random person effect, using SAS Proc Nlmixed (SAS version 8, 1999; SAS Institute). The fixed effects for both types of models were study type (hemodilution *vs.* control), condition (baseline, 5–6 g/dl hemoglobin breathing room air, 5–6 g/dl hemoglobin breathing oxygen), and an interaction between study type and condition.

Results

The volunteers were aged 28.4 ± 3.8 yr (mean \pm SD), were 1.70 ± 0.09 m tall, and weighed 64.4 ± 9.5 kg. There were 21 women and 10 men. Values for the tests of cognitive function and memory at the initial hemoglo-

Table 1. Test Values at Initial Hemoglobin Concentration of 12.7 g/dL

Variable	Mean	SD
Horizontal addition (s)	2.54	0.56
DSST (s)	1.96	0.32
Immediate memory (% not recalled)	44.7	14.4
Delayed memory (% not recalled)	57.0	16.7

DSST = Digit-Symbol Substitution Test; SD = standard deviation.

bin concentration are shown in table 1. Hemoglobin concentration before hemodilution was 12.7 ± 1.0 g/dl, and was 5.7 ± 0.3 g/dl when tested after hemodilution breathing room air and 5.7 ± 0.3 g/dl when breathing oxygen. Breathing oxygen at hemoglobin concentration of 5.7 g/dl increased arterial oxygen pressure (P_{aO_2}) to 406 ± 47 mmHg ($P < 0.001$; table 2). Arterial carbon dioxide pressure (P_{aCO_2}) was slightly lower ($P < 0.001$) and arterial pH slightly higher ($P < 0.001$) at the low hemoglobin concentration when the volunteers breathed oxygen in comparison to when they breathed room air (table 2). The order of test gas (oxygen or room air) did not affect the results.

Tests of Cognitive Function

Reduction of hemoglobin concentration or administration of oxygen did not alter the error rate for either test, except at one time: an increase in errors for horizontal addition on the control day at the time equivalent to that for hemoglobin concentration of 5.7 g/dl when the volunteers breathed room air compared with the time equivalent to the baseline test ($P < 0.025$). Reduction of hemoglobin concentration of the 31 volunteers to 5.7 g/dl when breathing room air increased the reaction time ($P < 0.05$) for the DSST (fig. 1A). Breathing oxygen improved the DSST reaction time ($P < 0.02$) to a value not different from that at the baseline hemoglobin concentration of 12.7 g/dl ($P = 0.96$; fig. 1A). Comparison of the data from the 10 volunteers between the experimental and control days confirmed these findings (fig. 1B). Reduction of hemoglobin concentration of the 31 volunteers to 5.7 g/dl when breathing room air or oxygen similarly ($P > 0.15$) decreased the reaction time ($P < 0.05$) for the horizontal addition test. The analysis that provided an attempt at correction for incorrect answers yielded similar results. However, when comparing the

Table 2. Arterial Blood Gas and pH Values

Variable	Hb = 12.7	Hb = 5.7 (Oxygen)	Hb = 5.7 (RA)
P_{aO_2} (mmHg)	104 ± 16	406 ± 47	108 ± 12
P_{aCO_2} (mmHg)	39.2 ± 3.8	36.5 ± 4.2	38.6 ± 4.8
pHa (units)	7.40 ± 0.03	7.46 ± 0.03	7.45 ± 0.03
Base-excess (mEq/l)	0.4 ± 1.6	3.1 ± 1.8	3.2 ± 1.6

Hb = hemoglobin; RA = room air; P_{aO_2} = arterial partial pressure of oxygen; P_{aCO_2} = arterial partial pressure of carbon dioxide.

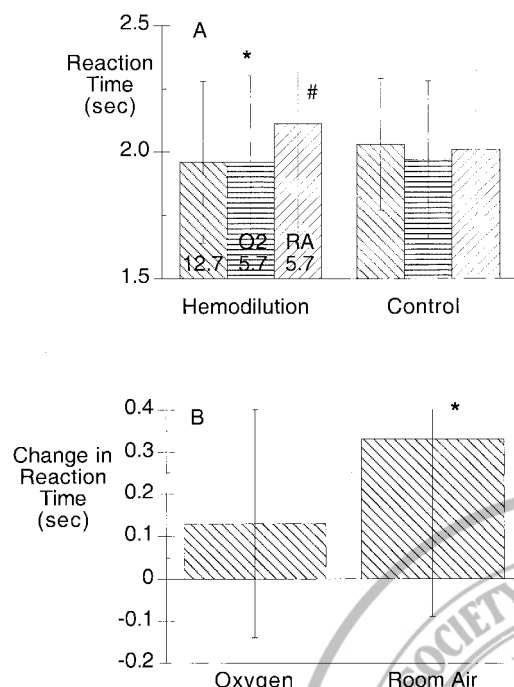


Fig. 1. (A) Reaction time for the digit-symbol substitution test (DSST) increased at hemoglobin concentration of 5.7 g/dl when breathing room air (▨) compared with the reaction time at hemoglobin concentration of 12.7 g/dl (□; # $P < 0.05$). Increasing P_{aO_2} to 406 mmHg by breathing oxygen (▤) decreased the reaction time (* $P < 0.02$ vs. breathing room air at hemoglobin 5.7 g/dl) to a value not different from that at hemoglobin concentration of 12.7 g/dl ($P = 0.96$). Data are mean \pm SD. Hemodilution data are from 31 volunteers, and control data are from 10 volunteers. (B) Comparison of DSST data from the 10 volunteers who were studied on hemodilution and control days. Reaction time increased at hemoglobin concentration of 5.7 g/dl when breathing room air, but not oxygen, compared with the reaction time at hemoglobin concentration of 12.7 g/dl. * $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the hemoglobin concentration of 5.7 g/dl and the baseline hemoglobin concentration of 12.7 g/dl. Data are mean \pm SD, $n = 10$.

data from the 10 volunteers between the experimental and control days, there was no effect of acute anemia on the reaction time of the horizontal addition test ($P > 0.4$).

Tests of Memory

Reduction of hemoglobin concentration to 5.7 g/dl did not alter immediate memory ($P = 0.4$), nor did breathing oxygen at the low hemoglobin concentration alter immediate memory ($P > 0.8$). When comparing the data from the 10 volunteers between the experimental and control days, delayed memory was degraded at a hemoglobin concentration 5.7 g/dl when breathing room air in comparison to the test at hemoglobin concentration of 12.7 g/dl ($P < 0.05$; fig. 2). Breathing oxygen improved delayed memory at hemoglobin concentration 5.7 g/dl in comparison with breathing room air ($P = 0.01$; fig. 2) to a value not different from that at hemoglobin concentration 12.7 g/dl.

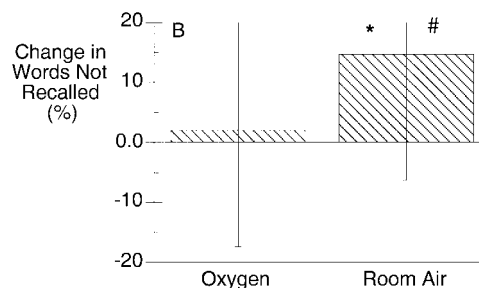


Fig. 2. Comparison of delayed memory data from the 10 volunteers who were studied on hemodilution and control days. Delayed memory was degraded at hemoglobin concentration of 5.7 g/dl when breathing room air, but not oxygen, compared with delayed memory at hemoglobin concentration of 12.7 g/dl. # $P < 0.05$ for comparison of the difference between experimental and control days for the difference between the value at the hemoglobin concentration of 5.7 g/dl and the baseline hemoglobin concentration of 12.7 g/dl. * $P < 0.01$ for comparison of the difference between experimental and control days for the difference when breathing room air compared with when breathing oxygen. Data are mean \pm SD, $n = 10$.

Reduction of hemoglobin concentration from 12.7 to 5.7 g/dl when the volunteers breathed room air decreased mean arterial blood pressure from 82.8 ± 8.9 to 73.4 ± 8.7 mmHg ($P = 0.0002$; fig. 3) and increased heart rate from 67.7 ± 11.5 to 90.5 ± 10.7 beats/min ($P < 0.0001$; fig. 3). Breathing oxygen at the low hemoglobin concentration did not change mean arterial pressure ($P > 0.95$) but significantly decreased heart rate to 82 ± 10 beats/min ($P < 0.0001$; fig. 3).

The subject's self-rated sense of energy declined when breathing room air at a hemoglobin concentration of 5.7 g/dl ($P < 0.001$; fig. 4). Breathing oxygen did not change this value ($P > 0.3$). Examining the data from the 10 volunteers who were also studied on a control day produced similar results.

The repeated-measures models confirmed the above statistical analyses.

Discussion

We confirmed our previous finding that acute isovolemic anemia subtly slows human reaction time and degrades memory,⁷ increases heart rate,⁵ and decreases self-assessed energy level.¹⁰ In the previous studies we showed that transfusion of erythrocytes is efficacious in reversing the effects of acute anemia on reaction time and memory⁷ and sense of energy.¹⁰ We have now shown that increasing oxygen delivery by another means, by increasing P_{aO_2} to approximately 400 mmHg by breathing oxygen, is similarly efficacious for reversing the effects of acute anemia on reaction time, memory, and heart rate, but not perceived energy level.

In our previous study we found that the effects of acute anemia were readily reversed by transfusing erythrocytes and increasing the hemoglobin concentration to 7 g/dl. In formulating our hypothesis for this study, we

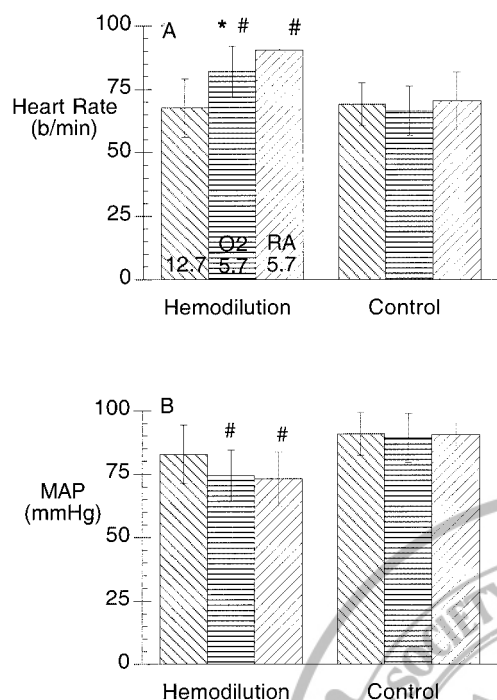


Fig. 3. (A) Heart rate increased at hemoglobin concentration of 5.7 g/dl when breathing room air (▨; $\#P < 0.0001$) compared with the heart rate at a hemoglobin concentration of 12.7 g/dl (▤). Breathing oxygen at a hemoglobin concentration of 5.7 g/dl decreased heart rate (▥; $\ast P < 0.0001$) compared with breathing room air, to a value that remained different from baseline ($\#P < 0.0001$). Heart rate did not change on the control day. Data are mean \pm SD. Hemodilution data are from 31 volunteers, and control data are from 10 volunteers. (B) Mean arterial blood pressure (MAP) decreased at a hemoglobin concentration of 5.7 g/dl when breathing room air (▨; $\ast P = 0.0002$) or oxygen (▥; $\ast P < 0.015$) compared with the MAP at a hemoglobin concentration of 12.7 g/dl (▤). MAP did not differ at a hemoglobin concentration of 5.7 g/dl when breathing room air versus oxygen ($P > 0.9$). MAP did not change on the control day. Data are mean \pm SD. Hemodilution data are from 31 volunteers, and control data are from 10 volunteers.

reasoned that increasing P_{aO_2} to values of 350 mmHg or more should provide an amount of oxygen equivalent to augmenting hemoglobin concentration by more than 2 g/dl. This would increase the "effective hemoglobin concentration" from a value of 5.5–6 g/dl to at least 7 g/dl. Based on preliminary data we anticipated that breathing oxygen would increase the volunteer's P_{aO_2} to approximately 350 mmHg. The difference in the amount of oxygen dissolved in plasma at a partial pressure of oxygen of 350 mmHg compared with 100 mmHg is 0.78 volumes of oxygen/dl (vol%) $\{(350 - 100) \cdot 0.0031\}$. Mixed-venous oxyhemoglobin saturation in similar volunteers at a similar hemoglobin concentration was 74%, with a P_{aO_2} of 37 mmHg.⁵ Each gram of hemoglobin releases 0.32 vol% oxygen when the arterial oxygen saturation of 98% is decreased to the mixed-venous oxygen saturation of 74% $\{1.34 \cdot (0.98 - 0.74)\}$. The amount of oxygen supplied by the plasma of the volunteers breathing room air was only 0.21 vol% $\{(104 - 37 \text{ mmHg}) \cdot 0.0031\}$. The volunteers' P_{aO_2} when breath-

ing oxygen was 406 mmHg. The difference between the dissolved oxygen at P_{aO_2} 406 mmHg and that at the measured value of 104 mmHg when the volunteers breathed room air is 0.94 vol% $\{(406 - 104 \text{ mmHg}) \cdot 0.0031\}$, a value equivalent to the amount of oxygen released by 2.94 g/dl $(0.94/0.32)$ of hemoglobin when blood passes from the arterial to the venous circulation. Hyperoxia caused by breathing oxygen might have reduced cardiac output. However, we did not measure cardiac output, nor are we aware of such data in unmedicated humans breathing oxygen while severely anemic. Our previous data indicate that, for the hemoglobin concentration range of 6–8 g/dl, cardiac output decreases approximately 5% for each gram of hemoglobin increase, without a change in oxygen consumption.⁵ Performing calculations similar to those above and including these effects, we estimated that producing a P_{aO_2} of 406 mmHg during severe anemia would produce a mixed-venous P_{O_2} of approximately 50 mmHg, resulting in a hemoglobin equivalence of 2.78 g/dl when breathing oxygen during severe anemia.

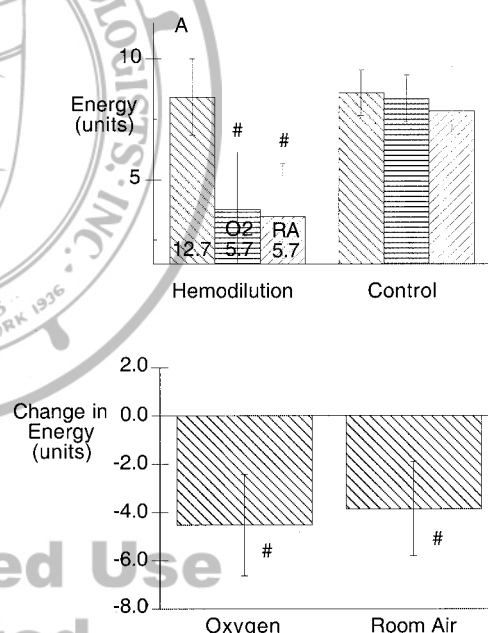


Fig. 4. (A) Self-assessed energy level decreased at hemoglobin concentration of 5.7 g/dl when breathing room air (▨; $\ast P < 0.0001$) or oxygen (▥; $\ast P < 0.0001$) compared with the self-assessed energy level at a hemoglobin concentration of 12.7 g/dl (▤). Increasing P_{aO_2} to 406 mmHg by breathing oxygen (▥) did not alter the self-assessed energy level at a hemoglobin concentration of 5.7 g/dl ($P > 0.3$). Data are mean \pm SD. Hemodilution data are from 31 volunteers, and control data are from 10 volunteers. (B) Comparison of self-assessed energy level data from the 10 volunteers who were studied on hemodilution and control days. Self-assessed energy level decreased at hemoglobin concentration of 5.7 g/dl when breathing room air or oxygen compared with that at hemoglobin concentration of 12.7 g/dl. $\ast P < 0.0001$ for comparison of the difference between experimental and control days for the difference between the value at the hemoglobin concentration of 5.7 g/dl and the baseline hemoglobin concentration of 12.7 g/dl. Data are mean \pm SD, $n = 10$.

Inasmuch as we previously found that acute reduction of hemoglobin concentration to 7 g/dl had no effect on the tests of information processing or memory,⁷ we hypothesized that breathing oxygen at a hemoglobin concentration of approximately 5.5–6 g/dl would reverse any deficits found at that hemoglobin concentration when breathing room air and provide results not different from those at the baseline hemoglobin concentration.

Our hypothesis that increasing P_{aO_2} to 350 mmHg or more would reverse the effects of acute severe anemia (hemoglobin concentration of 5.7 g/dl) on cognitive function and memory was supported by the results of the DSST and delayed memory test.

In the current study, the reaction time of the test of horizontal addition was not slowed at a hemoglobin concentration of 5.7 g/dl, and thus it was not possible to demonstrate an effect of breathing oxygen. However, in our earlier study, the horizontal addition reaction time did slow at hemoglobin concentrations of 5.1 and 6.0 g/dl. The utility of the use of the reaction time of this test depends on a constant error rate for all test conditions. Unfortunately, our results are confounded by an unexpected, substantial, several-fold increase in errors of horizontal addition when the volunteers were tested during the control time equivalent to the time of "acute anemia." The increased error rate makes problematic an analysis of the test of reaction time for horizontal addition.

The immediate memory test was not degraded in the current study at a hemoglobin concentration of 5.7 ± 0.3 g/dl, and thus demonstration of an effect of oxygen was not possible. In our earlier study, immediate memory was degraded at a hemoglobin concentration of 5.1 ± 0.2 g/dl but not at 6.0 ± 0.2 g/dl.⁷ Thus, the current results extend those of our earlier study and suggest that the threshold for degradation of this test by acute isovolemic anemia is at a hemoglobin concentration between 5.1 and 5.7 g/dl, which is lower than the threshold for degradation of the test of delayed memory.

Acute anemia decreases perceived energy level.¹⁰ The decrease of self-assessed energy level in the current study was similar to that found in our earlier report.¹⁰ However, unlike the tests of cognitive function and memory, breathing oxygen with a resultant substantial increase in P_{aO_2} had no effect on self-assessed energy level. Self-assessed energy level remained at a low level in comparison with the value at the baseline hemoglobin of 12.7 g/dl. In our earlier study, when the hemoglobin concentration of similar volunteers was increased from 5.1 to 7.2 g/dl by the erythrocyte transfusion, self-assessed energy level was improved to a value not different from that when the hemoglobin concentration was 7.2 g/dl during the production of acute anemia. It would appear that there may be a difference in the mechanism of production of the subjective sensation of fatigue and

the objective measurements of reaction time and memory. Alternatively, it is possible that reversal of the decreased perceived energy level may require a longer period of time than the 10–15 min that our volunteers breathed oxygen during severe anemia.

Acute isovolemic anemia in unmedicated humans increases heart rate, ventricular stroke volume, and cardiac index, and decreases mean arterial blood pressure.⁵ The heart rate and mean arterial pressure measured during acute isovolemic anemia at a hemoglobin concentration of 5.7 g/dl in this study are consistent with those described previously.⁵ In unmedicated humans, heart rate is an inversely linear function of hemoglobin concentration, increasing 4 beats/min for each 1-g/dl decrease of hemoglobin concentration.⁵ In the current study, the decrease in heart rate from 91 to 82 beats/min when oxygen was breathed at a hemoglobin concentration of 5.7 g/dl is consistent with the decrease expected if the effect of oxygen were equivalent to approximately 2–3 g/dl of hemoglobin,⁵ and is also similar to the recently reported heart rate during acute isovolemic anemia at a hemoglobin concentration of 8.6 g/dl.¹¹

The viscosity of blood with a hematocrit of 40% is approximately more than twice that of plasma and more than three times that of water. Decreasing the erythrocyte concentration decreases blood viscosity. The decreased mean arterial pressure noted with anemia is consistent with the relation between pressure and viscosity as described by Poiseuille.¹² However, the mathematical relation cannot be exactly applied to the circulation because of many factors, including nonuniform pulsatile blood velocity and the Fahraeus-Lindqvist effect (change of blood viscosity with change of velocity). Nevertheless, the lack of an effect of oxygen on mean arterial pressure during acute anemia is in keeping with the finding that the decreased mean arterial pressure is a result of decreased blood viscosity¹³ rather than a direct effect of inadequate oxygen content or delivery.

Our results have potential clinical implications. Postoperative tachycardia is associated with increased myocardial ischemia.^{14,15} If some or all of the tachycardia is caused by decreased arterial oxygen content, then in patients with coronary artery disease, myocardial ischemia could result from both the increased oxygen demand and decreased myocardial perfusion time imposed by the increased heart rate, and the decreased oxygen supply imposed by decreased oxygen content. Normal coronary arteries can dilate several-fold in response to acute anemia, maintaining normal myocardial oxygenation in conscious healthy dogs at hemoglobin concentrations of 5 g/dl.¹⁶ However, in the presence of coronary artery stenosis, myocardial ischemia occurs at a higher hemoglobin concentration than it does in the absence of stenoses.¹⁷ Administration of a β -adrenergic antagonist decreases postoperative myocardial ischemia,¹⁸ presumably by a heart rate-induced decreased

oxygen demand, and perhaps by decreased oxygen demand resulting from myocardial contractility as well. Oxygen may also have a salutary effect in a more general surgical population. Administration of oxygen to patients after abdominal surgery modestly increased arterial oxyhemoglobin saturation from 96 to 99% and decreased heart rate.¹⁹ The 3% increase in arterial oxygen saturation found by Rosenberg-Adamsen *et al.*¹⁹ in post-operative patients given oxygen would have added an amount of hemoglobin-bound oxygen equivalent to that carried by approximately 0.4 g/dl of hemoglobin. This would account for a heart rate decrease of approximately half the 3-beats/min decrease noted in that study. The remainder of the decrease could have been a result of the added oxygen dissolved in the plasma. However, the P_{aO_2} and hemoglobin concentration of those patients were not reported.

In summary, we found that improving arterial oxygen content by administration of oxygen is as efficacious as transfusion of erythrocytes in reversing the subtle cognitive function and memory deficits created by acute severe isovolemic anemia (hemoglobin concentration of 5.7 g/dl) in unmedicated humans.

References

1. Cain SM: Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *Am J Physiol* 1965; 209:604-10.
2. Cain SM: Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol* 1977; 42:228-34.
3. Adams RP, Dieleman LA, Cain SM: A critical value for O_2 transport in the rat. *J Appl Physiol* 1982; 53:660-4.
4. Van Woerkens ECSM, Trouwborst A, van Lanschott JJB: Profound hemodilution: What is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? *Anesth Analg* 1992; 75:818-21.
5. Weiskopf R, Viele M, Feiner J, Kelley S, Lieberman J, Noorani M, Leung J, Fisher D, Murray W, Toy P, Moore M: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998; 279:217-21.
6. Lieberman JA, Weiskopf RB, Kelley SD, Feiner J, Noorani M, J. L, Toy P, Viele M: Critical oxygen delivery in conscious humans is less than $7.3 \text{ ml} \cdot O_2^{-1} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. *ANESTHESIOLOGY* 2000; 92:407-13.
7. Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner J, Watson JJ, Hopf H, Toy P: Acute severe isovolemic anemia impairs cognitive function and memory and humans. *ANESTHESIOLOGY* 2000; 92:1646-52.
8. Lezak MD: *Neuropsychological Assessment*, 3rd Edition. New York, Oxford University Press, 1995, pp 438-9.
9. Shapiro SS, Wilk MB: An analysis of variance test for normality (complete samples). *Biometrika* 1965; 52:591-611.
10. Toy P, Feiner J, Viele M, Watson J, Yeap H, Weiskopf R: Fatigue during acute isovolemic anemia in healthy resting humans. *Transfusion* 2000; 40:457-60.
11. Ickx BE, Rigolet M, Van der Linden PJ: Cardiovascular and metabolic response to acute normovolemic anemia. *ANESTHESIOLOGY* 2000; 93:1001-16.
12. Poiseuille JL: Recherches expérimentales sur le mouvement des liquides dans les tubes de très petits diamètres. *Mémoires présentés par divers savants étrangers à l'Académie des Sciences Paris* 1846; 9:433-543.
13. Murray JF, Escobar E, Rapaport E: Effects of blood viscosity on hemodynamic responses in acute normovolemic anemia. *Am J Physiol* 1969; 216:638-42.
14. Mangano DT, Browner WS, M. H, London MJ, Tubau JF, Tateo IM, the Study of Perioperative Ischemia Research Group: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990; 323:1781-8.
15. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, Tubau JF, Krupski WC, the Study of Perioperative Ischemia Research Group: Perioperative myocardial ischemia in patients undergoing noncardiac surgery—I: Incidence and severity during the 4 day perioperative period. *J Am Coll Cardiol* 1991; 17:843-50.
16. Von Restorff W, Hoffing B, Holtz J, Bassenge E: Effect of increased blood fluidity through hemodilution on coronary circulation at rest and during exercise in dogs. *Pflügers Arch* 1975; 357:15-24.
17. Levy P, Kim S, Eekel P, Chavez R, Ezz F, Gould S, Salem M, Crystal G: Limit to cardiac compensation during acute isovolemic hemodilution: Influence of coronary stenosis. *Am J Physiol* 1993; 265:H340-9.
18. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano D: Prophylactic atenolol reduces postoperative myocardial ischemia. *ANESTHESIOLOGY* 1998; 88:7-17.
19. Rosenberg-Adamsen S, Lie C, Bernhard A, Kehlet H, Rosenberg J: Effect of oxygen treatment on heart rate after abdominal surgery. *ANESTHESIOLOGY* 1999; 90:380-4.

Unauthorized Use
Prohibited