Anesthesiology
2000; 92:407–13

Critical Oxygen Delivery in Conscious Humans Is Less Than 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$

Jeremy A. Lieberman, M.D., Richard B. Weiskopf, M.D.,† Scott D. Kelley, M.D.,‡ John Feiner, M.D.,§ Mariam Noorani, B.S.,‖ Jacqueline Leung, M.D., M.P.H.,‡ Pearl Toy, M.D.,# and Maurene Viele, M.D.***

Background: **The "critical" level of oxygen delivery (DO_2) is the value below which DO_2 fails to satisfy the metabolic need for oxygen. No prospective data in healthy, conscious humans define this value. The authors reduced DO_2 in healthy volunteers in an attempt to determine the critical DO_2.**

Methods: **With Institutional Review Board approval and informed consent, the authors studied eight healthy, conscious volunteers, aged 19–25 yr. Hemodynamic measurements were obtained at steady state before and after profound acute isovolemic hemodilution with 5% albumin and autologous plasma, and again at the reduced hemoglobin concentration after additional reduction of DO_2 by an infusion of a β-adrenergic antagonist, esmolol.**

Results: **Reduction of hemoglobin from 12.5 ± 0.8 g/dl to 4.8 ± 0.2 g/dl (mean ± SD) increased heart rate, stroke volume index, and cardiac index, and reduced DO_2 (14.0 ± 2.9 to 9.9 ± 2.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; all $P < 0.001$). Oxygen consumption (VO_2; 3.0 ± 0.5 to 3.4 ± 0.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$) and plasma lactate concentration (0.50 ± 0.10 to 0.62 ± 0.16 mM; $P < 0.05$; n = 7) increased slightly. Esmolol decreased heart rate, stroke volume index, and cardiac index, and further decreased DO_2 (to 7.3 ± 1.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; all $P < 0.01$ *vs.* before esmolol). VO_2 (3.2 ± 0.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; $P > 0.05$) and plasma lactate (0.66 ± 0.14 mM; $P > 0.05$) did not change further. No value of plasma lactate exceeded the normal range.**

Conclusions: **A decrease in DO_2 to 7.3 ± 1.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ in resting, healthy, conscious humans does not produce evidence of inadequate systemic oxygenation. The critical DO_2 in healthy, resting, conscious humans appears to be less than this value. (Key words: Anemia; hemodilution; blood lactate; critical oxygen delivery; oxygen consumption; β-adrenergic antagonism; erythrocyte transfusion.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

OXYGEN-CARRYING capacity of blood should be augmented (for example, by erythrocyte transfusion) when oxygen delivery (DO_2) is not adequate to prevent tissue hypoxia. The DO_2 below which evidence of hypoxia is produced, *i.e.*, the "threshold," has been defined as the "critical" DO_2,[1,2] and has been determined in anesthetized dogs,[1,2] rats,[3] and pigs.[4,5] The value varies substantially among species, and anesthesia alters the value of the critical DO_2.

The critical DO_2 in humans is not known. A value for critical DO_2 of approximately 5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ was found in an elderly, anesthetized man, with neuromuscular blockade and mechanically ventilated lungs.[6] However, systematic prospective efforts to determine the critical DO_2 in humans have not been successful. Reduction of DO_2 to 10 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ by acute isovolemic hemodilution to a hemoglobin concentration of 5 g/dl in conscious, healthy, resting humans failed to produce evidence of inadequate systemic DO_2.[7]

Accordingly, we attempted to define the critical DO_2 in conscious, healthy adults by reducing DO_2 by acute isovolemic reduction of the hemoglobin concentration to 5 g/dl, followed by further reduction of DO_2 by decreasing cardiac output with a continuous infusion of a β-adrenergic antagonist.

* Assistant Professor. Current position: Assistant Professor, Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

† Professor, Department of Anesthesia.

‡ Associate Professor, Department of Anesthesia.

§ Assistant Professor, Department of Anesthesia.

‖ Staff Research Associate, Department of Anesthesia.

Professor, Department of Laboratory Medicine.

** Assistant Professor, Department of Laboratory Medicine.

Received from the Departments of Anesthesia, Physiology, and Laboratory Medicine, and The Cardiovascular Research Institute, University of California, San Francisco. Submitted for publication May 12, 1999. Accepted for publication September 20, 1999. Supported in part by the US Department of Defense, Frederick, Maryland (contract DAMD 17-95-C-5006), the National Heart, Lung and Blood Institute, Bethedsa, Maryland (grant 1 P50 HL54476), and the Anesthesia Research Foundation, San Francisco, California.

Address reprint requests to Dr. Weiskopf: Department of Anesthesia, University of California, 521 Parnassus Avenue, Room C450, San Francisco, California 94143-0648. Address electronic mail to: weiskopf@jemo.ucsf.edu

Methods

With approval of the Institutional Review Board and with informed consent, we studied eight (five women, three men) healthy, paid volunteers. No volunteer smoked cigarettes or took prescription medications. All were without history of cardiovascular, pulmonary, or hepatic disease and had normal physical examination results. The data obtained at "baseline" and at a hemoglobin concentration of 5 g/dl for these eight volunteers were included as part of a larger group (n = 32) in a previous report.[7]

The methods for producing acute isovolemic hemodilution have been previously described.[7] Briefly, peripheral venous and radial artery cannulae were inserted into each subject using 1% lidocaine local anesthesia. A flow-directed pulmonary artery cannula (Baxter Healthcare, Glendale, CA) was inserted *via* the right internal jugular vein. Propofol (50–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenous) was infused briefly to provide sedation during placement of the pulmonary artery cannula. After all cannulae were inserted and the propofol infusion was discontinued, the subjects rested for 30 min before measurement of any variables. Cardiac output was measured by thermodilution (duplicate, or triplicate if duplicates differed by > 10%; A/S3 Datex Medical Instrumentation, Tewksbury, MA). As blood was removed, isovolemia was maintained, as judged by constant central venous and pulmonary capillary wedge pressures, by infusion of 5% human serum albumin (Baxter Healthcare) and the subject's platelet-rich plasma as it became available after separation from the erythrocytes of the removed blood. At the times of cardiovascular measurements, arterial and mixed venous blood was sampled for measurement of *p*H, oxygen content, and oxyhemoglobin saturation (OSM3 Hemoximeter; Radiometer, Copenhagen, Denmark) and arterial plasma lactate concentration (YSI No 0.2700; Yellow Springs Instrument Co., Yellow Springs, OH). Cardiac index, stroke volume index, systemic vascular resistance index, DO_2, and oxygen consumption (VO_2) were calculated using standard formulae. The subject's pulmonary artery temperature was maintained at 37°C by body surface warming with heated air (Bair Hugger model 1200; Augustine Medical Inc., Eden Prairie, MN) and by warming of the infused fluids.

Measurements were made 30 min after insertion of invasive cannulae and before removal of blood (baseline); after isovolemic hemodilution to a hemoglobin concentration of 5 g/dl; and again after 15 min steady-state reduction of the heart rate (HR) to approximately 85% of that at the end of hemodilution, achieved by an intravenous infusion of esmolol (50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to an *a priori* maximum of 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$) without infusion of additional fluid. All erythrocytes were transfused after the conclusion of the experiment (no measurements made) and a physician examined all subjects the following morning before discharge.

Electrocardiography (ECG; five-lead) and a three-channel Holter ECG was monitored in all subjects (Del Mar model 459; Del Mar Avionics, Irvine, CA). The Holter monitor recorded continuously from 1 h before start of the study until completion of the study. The frequency response of the Holter recorder met the American Heart Association specification for ST changes, the cutoff limit being 0.05 Hz for low frequency and 100 Hz for high frequency. For Holter monitoring, three bipolar leads—CC5, modified CM5, and ML—were used. Each ECG recording on Holter tapes was scanned visually using an ECG analysis system (Del Mar model 750). All normal QRS complexes were identified, and all abnormal QRS complexes (*e.g.*, ventricular ectopic beats and conduction abnormalities) were excluded from ST-segment analysis. Continuous ST-segment trends were generated for the entire tape. All possible ischemic episodes were reviewed and verified by an investigator who was blinded to patient identity, hemoglobin concentration, and administration of esmolol. Prospective criteria for an ischemic episode were defined as a reversible ST-segment shift from baseline of 0.1 mV or greater depression at J+ 60 ms or 0.2 mV or greater elevation at the J point lasting for at least 1 min. The time after the J point chosen to measure ST-segment depression was adjusted to exclude T wave during tachycardia.

Statistical Analysis

All data are expressed as the mean ± SD. Data obtained during esmolol infusion were compared with data obtained at the end of hemodilution (5 g/dl) and at baseline by analysis of variance with repeated measures and a *post hoc* Newman-Keuls test. Statistical significance was accepted at $P < 0.05$.

Results

Volunteers were 21.9 ± 2.2 yr old (mean ± SD), weighed 68 ± 13 kg, and had an estimated body surface area of 1.81 ± 0.23 m^2. The duration of the experiment was 190 ± 39 min.

Isovolemic hemodilution reduced hemoglobin concen-

Table 1. Responses to Reduction of Oxygen Delivery

Variable	Baseline	End of Hemodilution	Esmolol Infusion
Hemoglobin (g/dl)	12.5 ± 0.8	4.8 ± 0.2*	4.7 ± 0.2*
Ca_{O_2} (g/dl)	16.9 ± 1.0	6.7 ± 0.3†	6.6 ± 0.2†
MAP (mmHg)	85 ± 10	70 ± 7*	61 ± 8*‡
HR (beats/min)	65 ± 14	90 ± 15*	80 ± 13*‡
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.1 ± 0.6	5.4 ± 0.9*	4.1 ± 0.5*‡
SVI (ml/m^{-2})	47.8 ± 3.5	60.9 ± 5.8*	51.8 ± 4.1§‖
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^2$)	2150 ± 600	950 ± 110*	1050 ± 160*
CVP (mmHg)	6 ± 2	6 ± 3	8 ± 3*‖
PCWP (mmHg)	9 ± 2	9 ± 2	12 ± 3§#
DO_2 ($ml\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	14.0 ± 2.9	9.9 ± 2.0*	7.3 ± 1.4*‖
VO_2 ($ml\ O_2 \cdot kg^{-1} \cdot min^{-1}$)	3.0 ± 0.5	3.4 ± 0.6†	3.2 ± 0.6
Arterial *p*H (U)	7.39 ± 0.01	7.44 ± 0.02*	7.44 ± 0.03*
Mixed venous *p*H (U)	7.36 ± 0.01	7.41 ± 0.02*	7.40 ± 0.02*
Pa_{CO_2} (mmHg)	42 ± 4	42 ± 4	41 ± 6
Pv_{CO_2} (mmHg)	47 ± 4	47 ± 4	47 ± 4
Base-excess (mEq/l)	1.2 ± 2.0	4.4 ± 2.4*	4.1 ± 2.4*
Plasma lactate (mM)	0.50 ± 0.10	0.62 ± 0.16†	0.66 ± 0.14§
Sv_{O_2} (%)	77.8 ± 4.6	67.3 ± 8.0*	56.8 ± 7.6*‖
Pv_{O_2} (mmHg)	48 ± 4	37 ± 3†	33 ± 3*‖
Extraction ratio (VO_2/DO_2)	0.22 ± 0.04	0.35 ± 0.08*	0.44 ± 0.08*‖

Ca_{O_2} = arterial oxygen content; MAP = mean arterial blood pressure; HR = heart rate; CI = cardiac index; SVI = stroke volume index; SVRI = systemic vascular resistance index; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; DO_2 = oxygen delivery; VO_2 = oxygen consumption; Sv_{O_2} = mixed venous oxyhemoglobin saturation; Pv_{O_2} = mixed venous PO_2.

P values *vs.* baseline: † < 0.05; § < 0.01; * < 0.001;

P values *vs.* end of hemodilution: # < 0.05; ‡ < 0.01; ‖ < 0.001.

tration from 12.5 ± 0.8 to 4.8 ± 0.2 g/dl (table 1; $P < 0.001$). Heart rate, stroke volume index, and cardiac index increased (cardiac index: from 3.1 ± 0.6 $l \cdot min^{-1} \cdot m^{-2}$ to 5.4 ± 0.9 $l \cdot min^{-1} \cdot m^{-2}$; $P < 0.001$), but not sufficiently to prevent DO_2 from decreasing (from 14.0 ± 2.9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ to 9.9 ± 2.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$).

Infusion of esmolol after hemodilution, without additional hemodilution or infusion of fluid, did not change further the hemoglobin concentration (4.7 ± 0.2 g/dl; $P > 0.05$), but decreased cardiac index by 24 ± 6% to 4.1 ± 0.5 $l \cdot min^{-1} \cdot m^{-2}$ ($P < 0.001$), as a result of an 11 ± 5% decrease in HR ($P < 0.01$) and a 15 ± 6% decrease in stroke volume index ($P < 0.001$). Thus, esmolol reduced DO_2 to 7.3 ± 1.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$), which is equivalent to 274 ± 51 ml $O_2 \cdot min^{-1} \cdot m^{-2}$.

Acute isovolemic hemodilution increased VO_2 from the baseline value of 3.0 ± 0.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ to 3.4 ± 0.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$). Further reduction of DO_2 by esmolol infusion did not change VO_2 (3.2 ± 0.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; $P > 0.05$; fig. 1). The relation of DO_2 and VO_2 for each subject is depicted in figure 2, and the change in VO_2 from baseline as a function of DO_2 is shown in figure 3. Only two of eight volunteers had values of VO_2 that were less than their individual baseline values. For one of these two volunteers, VO_2 subsequently increased at a lower DO_2.

One sample for lactate determination for one volunteer was lost; consequently, data for plasma lactate concentrations are reported for seven volunteers. Plasma

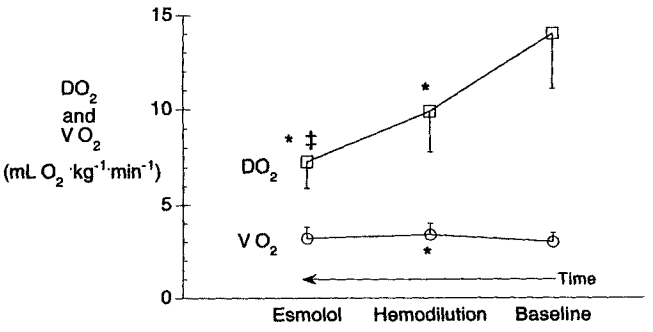

Fig. 1. Oxygen delivery (DO_2) and oxygen consumption (VO_2) in eight healthy adults before (hemoglobin concentration, 12.5 ± 0.8 g/dl) and after (hemoglobin concentration, 4.8 ± 0.2 g/dl) isovolemic hemodilution and during intravenous infusion of a β-adrenergic antagonist, esmolol (with hemoglobin concentration of 4.7 ± 0.2 g/dl). *Indicates $P < 0.05$ *versus* baseline; ‡Indicates $P < 0.05$ *versus* hemodilution without esmolol.

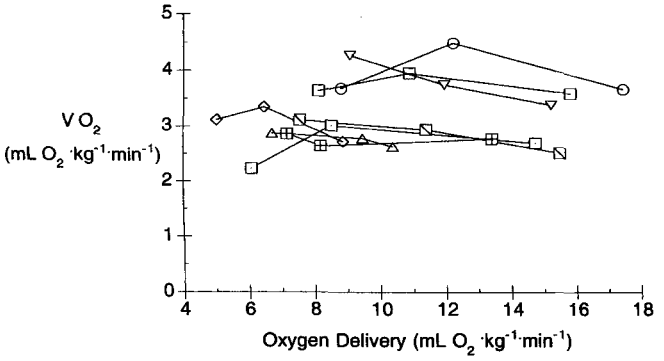

Fig. 2. Relation of oxygen consumption (VO_2) to oxygen delivery (DO_2) in all subjects. A critical DO_2 was not detected.

lactate concentrations after hemodilution (0.62 ± 0.16 mM) and during esmolol infusion (0.66 ± 0.14 mM) were minimally, but statistically significantly, greater than those at baseline (0.53 ± 0.13 mM; $P < 0.05$), but did not differ from each other ($P > 0.05$). No plasma lactate concentration exceeded the upper limit of normal (fig. 4).

Arterial and mixed venous *p*H and base-excess did not change from baseline ($P > 0.05$; table 1). Mixed venous oxygen saturation (Sv_{O_2}) decreased from 77.8 ± 4.6% to 67.3 ± 8.0% with hemodilution ($P < 0.001$) and subsequently to 56.8 ± 7.6% ($P < 0.001$) as DO_2 decreased further with esmolol infusion. The oxygen extraction ratio (VO_2/DO_2) increased from 0.22 ± 0.04 to 0.35 ± 0.08 with hemodilution ($P < 0.001$) and to 0.44 ± 0.08 ($P < 0.001$) with infusion of esmolol.

No ST changes were observed in the real-time monitored ECG. The Holter tapes of all subjects were able to be analyzed. A single episode that met the criteria for significant ST changes occurred in a 25 yr old woman. A 0.11-mV ST depression occurred during the final stage of hemodilution, during the time that the hemoglobin was

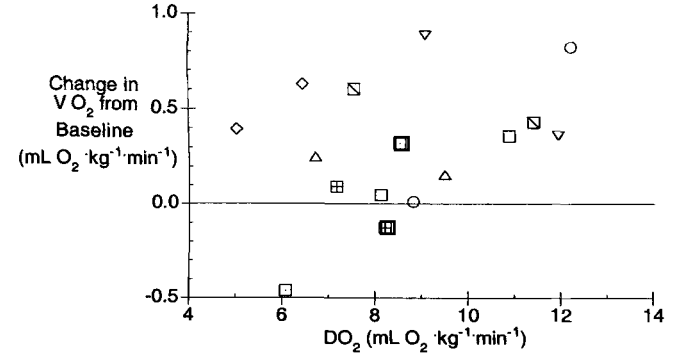

Fig. 3. Change in oxygen consumption (VO_2) from baseline during states of reduced oxygen delivery (DO_2) for each volunteer, represented by a unique symbol. At the lowest DO_2 for each subject, only one subject had a lower VO_2 than at baseline.

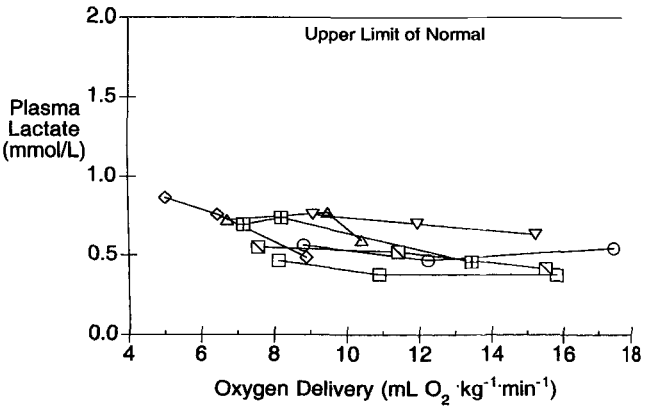

Fig. 4. Plasma lactate concentrations for seven subjects at normal and reduced oxygen delivery (DO_2). No value exceeded the upper limit of normal.

reduced from 5.3 to 4.6 g/dl. DO_2 was 10.9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and VO_2 was 3.9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, which was not less than the baseline value of 3.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. These ST changes resolved with initiation of the esmolol infusion, reduction of HR from 110 to 89 beats/min, and decrease of DO_2 from 10.9 to 8.1 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. No subject reported any cardiac symptoms. One subject complained of transient light-headedness and fatigue during the esmolol infusion; a second subject felt a "sense of dread." No other symptoms related to decreased DO_2 or tissue hypoxia were reported, and all symptoms resolved promptly after discontinuation of the administration of esmolol and infusion of the subjects' erythrocytes.

Discussion

We reduced DO_2 from 14 to 10 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, with acute reduction of hemoglobin to 4.7 g/dl, and further to 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ by infusion of a β-adrenergic antagonist, esmolol, in conscious, healthy, resting adults. The DO_2 at a hemoglobin concentration of 5 g/dl is similar to the value we reported from a larger group at this level of acute isovolemic anemia.[7] The addition of an infusion of a β-adrenergic antagonist reduced DO_2 to a value substantially less than that achieved previously. Despite this nearly 50% reduction of DO_2 from baseline, we were unable to demonstrate inadequate systemic oxygenation as assessed by our two primary measures: VO_2 did not decrease, and the tiny increases in plasma lactate concentrations at a hemoglobin concentration of 5 g/dl with and without esmolol infusion are not physiologically important. All plasma

lactate values were within normal limits (upper limit, 2 mM): the highest concentration was 0.87 mM, and the mean change was less than 0.2 mM.

Only one woman had a single transient ST-segment change during the study period. It was not symptomatic and resolved despite a further reduction in DO_2. This change may have been secondary to myocardial ischemia or may have been an elevated HR-induced benign ECG change. The resolution of the ST depression during administration of esmolol may have been a result of a decrease in the HR from 110 to 89 beats/min, which should have reduced myocardial VO_2 by approximately 22%.[8] In dogs, the critical myocardial DO_2 and the systemic critical DO_2 are reached at the same hemoglobin concentration.[9] The absence of evidence for inadequate global DO_2 and the low specificity of ECG changes in the absence of other evidence of cardiac disease,[10,11] especially in young women,[12,13] are suggestive that this single ECG change was more likely benign and HR-induced rather than representative of myocardial ischemia.

Plasma lactate concentration is an established marker of inadequate systemic DO_2.[1,2] In experiments of decreased DO_2, plasma lactate concentration increases simultaneously with decreases of VO_2, a primary marker of inadequate DO_2. The statistically significant, but physiologically unimportant increase in plasma lactate at the lowest levels of DO_2 that we achieved could indicate that DO_2 was beginning to approach the level at which plasma lactate concentration increases substantially with further decreases of DO_2. If that were true, VO_2 should have begun to decrease at that point to values below those at baseline. In a group of 32 healthy adults in whom DO_2 was decreased to 10.7 ± 2.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, plasma lactate concentration did not increase.[7] In the current study, plasma lactate concentration increased minimally when DO_2 was reduced to 9.9 ± 2.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ but did not increase further when DO_2 was decreased further to 7.3 ± 1.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. This suggests that the volunteers did not reach their critical DO_2. Alternatively, it is possible that these tiny increases reflect decreased hepatic clearance of lactate. However, hepatic clearance of lactate does not appear to decrease until systemic oxygenation is inadequate. In anesthetized dogs, hepatic blood flow increases, but not as much as does cardiac output, with acute anemia to a hematocrit of 17%, and the effect is not altered by β-adrenergic blockade.[14] The hepatic extraction ratio of bromsulphalein decreases, but clearance increases.[14] Hepatic clearance of lactate does not change in pigs anesthetized with ketamine and flunitrazepam and then made acutely anemic to hematocrit levels of 15%, despite a decrease in hepatic surface partial pressure of oxygen (P_{O_2}).[15,16] Hepatic uptake of lactate in those pigs did not decrease until systemic DO_2 was decreased, by the addition of isoflurane, from approximately 7–9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ to approximately 4 or 5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, values below the critical DO_2.[15] Furthermore, modeling of data obtained in humans suggests that, in the absence of increased lactate production, even large decreases of hepatic uptake of lactate will have only small effects on plasma lactate concentrations.[17] The increase in base-excess with acute reduction of DO_2 to 9.9 ± 2.0 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ was probably a result of hepatic metabolism of the citrate present in the transfused autologous plasma. This adds further support to our thought that hepatic clearance and metabolism continued during this period. Alternatively, it is possible that our method of measuring VO_2 was insufficiently sensitive to detect such a small change in VO_2.

The DO_2 we measured during acute anemia plus infusion of a β-adrenergic antagonist, 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (273 ml $O_2 \cdot min^{-1} \cdot m^{-2}$), is lower than any value reported in healthy, conscious humans. We previously demonstrated that a DO_2 of 10.7 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ in healthy conscious adults did not decrease VO_2 or increase plasma lactate concentration.[7] Patients with substantial coronary artery disease, anesthetized for coronary artery surgery do not have anaerobic myocardial metabolism with hemoglobin concentrations as low as approximately 6 g/dl.[18] A critical DO_2 reported by the authors to be 4.9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, which we calculated to be 5.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, was found in an 84-yr-old man, who was anesthetized and had pharmacologically induced neuromuscular blockade and mechanically ventilated lungs.[6] General anesthesia decreased his VO_2 by approximately 25%. Anesthesia, neuromuscular blockade, and mechanical ventilation of the lungs would have decreased the VO_2 and, thereby, the critical DO_2. In addition, modern inhaled halogenated anesthetics decrease myocardial contractility and myocardial VO_2,[19–21] and function and VO_2 of other organs, such as the brain.[22] Furthermore, the critical DO_2 in dogs is influenced by the type of anesthetic.[23] Therefore, critical DO_2 determined during anesthesia cannot be applied to the awake condition.

Similarly, although the critical DO_2 is known for anesthetized, mechanically ventilated dogs (9 or 10 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$),[1,2] rats (23 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$),[3] pigs (8–12 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$),[4,5] and baboons (3–6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$),[24] these values cannot be applied to con-

scious humans. The reduction of VO_2 by anesthetics and other drugs used in those experiments would have reduced the critical DO_2. In conscious, restrained, acutely instrumented baboons, a decrease in hematocrit to 15% and in DO_2 to 11 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ did not decrease VO_2.[25] The variation of critical DO_2 among the few species in which it has been determined makes application of the data to humans unreliable.

Our primary measures of whole-body VO_2 and blood lactate concentration are largely measures of adequacy of systemic oxygenation. Although VO_2 decreases in individual tissues and organs when DO_2 is inadequate, it is unlikely that we could have detected any decreased VO_2 in relatively small regions because of the error inherent in the measurement of VO_2. In addition, the use of cardiac output for the estimation of VO_2 has been criticized because of the potential problem of "mathematical coupling."[26] However, if the data contain a range for DO_2 that is relatively large compared with the measurement error, as occurred with our data (by a factor of 5 to 10), the effect of mathematical coupling is small.[27] In addition, the major influence of mathematical coupling is to erroneously indicate supply dependency of VO_2 when it is not truly present[27,28]; however, we did not find supply dependency of VO_2 in subjects in the current study.

Volunteers in the current study were severely anemic for approximately 1 h. It is possible that a longer period would have resulted in inadequate systemic oxygenation. Because, in addition to the oxygen in the lungs and erythrocytes, the body contains little stores of oxygen, any later development of inadequate oxygenation would have to result from a degradation of compensatory mechanisms. Analysis of human kinetic data for lactate production and clearance indicates that increased production resulting from tissue hypoxia should be detected in blood within the period of time in which the volunteers had severely decreased DO_2.[17]

We observed the volunteers at rest only, and therefore cannot speculate as to the possible critical DO_2 during mild-to-moderate exercise. Within a relatively narrow range, hemoglobin concentration (9.7 ± 0.9 to 10.7 ± 0.9 g/dl) does not affect ability to function after surgical repair of femur fractures,[29] nor does a somewhat larger range (approximately 8–12 g/dl) affect maximal duration of exercise after coronary artery surgery.[30] Mild anemia (11.5 g/dl) in young healthy adults decreases DO_2 to the legs during maximal, but not submaximal, exercise.[31]

We did not achieve our goal of determining the critical level of systemic DO_2. We studied only eight volunteers, although we originally planned a larger study. When it became apparent that we would not define the critical DO_2, we were constrained not to enroll additional volunteers. We used β-adrenergic antagonism to reduce DO_2 below that achieved by severe anemia alone because of our concern for the safety of the volunteers at hemoglobin concentrations less than 5 g/dl. The methodology should not have influenced the results because reduction of DO_2 by either anemia or β-adrenergic blockade produces identical critical DO_2 in dogs.[2] Only one subject had a final VO_2 less (by 17%) than his baseline VO_2. This occurred during the esmolol infusion, at a hemoglobin concentration of 4.5 g/dl and a DO_2 of 6.1 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ (250 ml $O_2 \cdot min^{-1} \cdot m^{-2}$). This subject did not have an abnormal blood lactate concentration and did not complain of any symptoms or have any abnormal ECG ST segments. It is possible that his DO_2 of 6.1 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ was just below his critical value, but we could not confirm that by either plasma lactate concentration or Holter recording.

In summary, we found that reducing DO_2 to 7.3 ± 1.4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ by acute isovolemic anemia (hemoglobin = 4.7 ± 0.2 g/dl) plus an infusion of a β-adrenergic antagonist in resting healthy adults aged 19–25 yr does not produce evidence of inadequate systemic oxygenation. This extends our previous finding and suggests that the decreased DO_2 associated with a hemoglobin concentration of 4.5–5 g/dl is well-tolerated by conscious, healthy, young, resting adults.

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 O2 transport in the rat. J Appl Physiol 1982; 53:660–4

4. Schou H, Perez de Sá V, Sigurdardóttir M, Roscher R, Jonmarker C, Werner O: Circulatory effects of hypoxia, acute normovolemic hemodilution, and their combination in anesthetized pigs. ANESTHESIOLOGY 1996; 84:1443–5

5. Van Woerkens ECSM, Trouwborst A, Duncker DJGM, Koning MMG, Boomsma F, Verdouw PD: Catecholamines and regional hemodynamics during isovolemic hemodilution in anesthetized pigs. J Appl Physiol 1992; 72:760–9

6. 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

7. 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

8. Von Restorff W, Hofling B, Holtz J, Bassenge E: Effect of increased blood fluidity through hemodilution on general circulation at rest and during exercise in dogs. Pflugers Arch 1975; 357:25-34

9. Jan KM, Chien S: Effect of hematocrit variations on coronary hemodynamics and oxygen utilization. Am J Physiol 1977; 233: H106-13

10. Borer JS, Brensike JF, Redwood DR, Itscoitz SB, Passamani ER, Stone NJ, Richardson JM, Levy RI, Epstein SE: Limitations of the electrocardiographic response to exercise in predicting coronary-artery disease. N Eng J Med 1975; 293:367-71

11. Froelicher VF, Thompson AJ, Longo MR Jr, Triebwasser JH, Lancaster MC: Value of exercise testing for screening asymptomatic men for latent coronary artery disease. Prog Cardiovasc Dis 1976; 18:265-76

12. Chaitman B, Hanson J: Comparative sensitivity and specificity of exercise electrocardiographic lead systems. Am J Cardiol 1981; 47: 1335-49

13. Cumming GR, Dufresne C, Samm J: Exercise ECG changes in normal women. CMAJ 1973; 109:108-11

14. Chamorro G, Rodriguez JA, Dzindzio B, Rapaport E: Effect of acute isovolemic anemia on cardiac output and estimated hepatic blood flow in the conscious dog. Circ Res 1973; 32:530-5

15. Nöldge GF, Priebe HJ, Geiger K: Splanchnic hemodynamics and oxygen supply during acute normovolemic hemodilution alone and with isoflurane-induced hypotension in the anesthetized pig. Anesth Analg 1992; 75:660-74

16. Nöldge GF, Priebe HJ, Bohle W, Buttler KJ, Geiger K: Effects of acute normovolemic hemodilution on splanchnic oxygenation and on hepatic histology and metabolism in anesthetized pigs. ANESTHESIOLOGY 1991; 74:908-18

17. Woods HF, Connor H, Tucker GT: The role of altered lactate kinetics in the pathogenesis of type B lactic acidosis, Metabolic Acidosis. Ciba Foundation Symposium 87. Edited by Porter R, Lawrenson G. London, The Pitman Press, 1982, pp 307-23

18. Doak GJ, Hall RI: Does hemoglobin concentration affect perioperative myocardial lactate flux in patients undergoing coronary artery bypass surgery? Anesth Analg 1995;80:910-6

19. Severinghaus JW, Cullen SC: Depression of myocardium and body oxygen consumption with fluothane. ANESTHESIOLOGY 1958; 19: 165-77

20. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Evaluation of myocardial contractility in the chronically instrumented dog with intact autonomic nervous system function: Effects of desflurane and isoflurane. Acta Anaesthesiol Scand 1993; 37:203-10

21. Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC: Direct negative inotropic and lusitropic effects of sevoflurane. ANESTHESIOLOGY 1994; 81:156-67

22. Drummond JC, Shapiro HM: Cerebral physiology, Anesthesia. Edited by Miller RD. New York, Churchill Livingstone, 1990, pp 621-58

23. Van der Linden P, Gilbart E, Engelman E, Schmartz D, Vincent JL: Effects of anesthetic agents on systemic critical O_2 delivery. J Appl Physiol 1991; 71:83-93

24. Wilkerson DK, Rosen AL, Gould SA, Sehgal LR, Sehgal HL, Moss GS: Oxygen extraction ratio: A valid indicator of myocardial metabolism in anemia. J Surg Res 1987; 42:629-34

25. Levine E, Rosen A, Sehgal L, Gould S, Sehgal H, Moss G: Physiologic effects of acute anemia: Implications for a reduced transfusion trigger. Transfusion 1990; 30:11-4

26. Archie J: Mathematic coupling of data: A common source of error. Ann Surg 1981; 193:296-303

27. Stratton H, Feustell P, Newell J: Regression of calculated variables in the presence of shared measurement error. J Appl Physiol 1987; 62:2083-93

28. Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russell JA: Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. Am J Resp Crit Care Med 1994; 150: 318-23

29. Carson J, Terrin M, Barton F, Aaron R, Greenburg A, Heck D, Magaziner J, Merlino F, Bunce G, McClelland B, Duff A, Noveck H: A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion 1998; 38:522-9

30. Johnson R, Thurer R, Kruskall M, Sirois C, Gervino E, Critchlow J, Weintraub R: Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992; 104:307-14

31. Koskolou M, Roach R, Calbet J, Radegran G, Saltin B: Cardiovascular responses to dynamic exercise with acute anemia in humans. Am J Physiol 1997; 273:H1787-93