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Human Cardiovascular and Metabolic Response to Acute, Severe Isovolemic Anemia

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Context.—Although concern over the risks of red blood cell transfusion has resulted in several practice guidelines for transfusion, lack of data regarding the physiological effects of anemia in humans has caused uncertainty regarding the blood hemoglobin (Hb) concentration requiring treatment.

Objective.—To test the hypothesis that acute isovolemic reduction of blood Hb concentration to 50 g/L in healthy resting humans would produce inadequate cardiovascular compensation and result in tissue hypoxia secondary to inadequate oxygen transport.

Design.—Before and after interventional study.

Setting.—Academic tertiary care medical center.

Participants.—Conscious healthy patients (n=11) prior to anesthesia and surgery and volunteers not undergoing surgery (n=21).

Interventions.—Aliquots of blood (450-900 mL) were removed to reduce blood Hb concentration from 131 (2) g/L to 50 (1) g/L [mean (SE)]. Isovolemia was maintained with 5% human albumin and/or autologous plasma. Cardiovascular parameters, arterial and mixed venous oxygen content, oxyhemoglobin saturation, and arterial blood lactate were measured before and after removal of each aliquot of blood. Electrocardiogram and, in a subset, Holter monitor were monitored continuously.

Main Outcome Measures.—"Critical" oxygen delivery ($\dot{T}O_2$) as assessed by oxygen consumption ($\dot{V}O_2$), plasma lactate concentration, and ST changes on electrocardiogram.

Results.—Acute, isovolemic reduction of Hb concentration decreased systemic vascular resistance and $\dot{T}O_2$ and increased heart rate, stroke volume, and cardiac index (each $P<.001$). We did not find evidence of inadequate oxygenation: $\dot{V}O_2$ increased slightly from a mean (SD) of 3.07 (0.44) mL of oxygen per kilogram per minute (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) to 3.42 (0.54) mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ ($P<.001$) and plasma lactate concentration did not change (0.81 [0.11] mmol/L to 0.62 [0.19] mmol/L; $P=.09$). Two subjects developed significant ST changes on Holter monitor: one apparently related to body position or activity, the other to an increase in heart rate (at an Hb concentration of 46-53 g/L); both occurred in young women and resolved without sequelae.

Conclusions.—Acute isovolemic reduction of blood Hb concentration to 50 g/L in conscious, healthy resting humans does not produce evidence of inadequate systemic $\dot{T}O_2$, as assessed by lack of change of $\dot{V}O_2$ and plasma lactate concentration. Analysis of Holter readings suggests that at this Hb concentration in this resting healthy population, myocardial ischemia would occur infrequently.

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THE MOST COMMON indication for the transfusion of red blood cells is to augment the oxygen-carrying capacity of the blood of an anemic patient. The potential for blood components to transmit infectious disease has produced concern and "guidelines," "practice parameters," or "standards" delineating conditions under which it is appropriate to transfuse red blood cells.[1-4] Formulation of these documents has been hindered by the lack of data defining the hemoglobin (Hb) concentration in humans that does not allow for adequate oxygen transport ($\dot{T}O_2$) and that initiates tissue hypoxia.

Accordingly, we acutely decreased the Hb concentration of 32 healthy resting humans to test the hypothesis that a blood Hb concentration of 50 g/L would result in tissue hypoxia secondary to inadequate $\dot{T}O_2$. We did not conduct these studies with the subjects performing any activity that would thereby increase oxygen consumption ($\dot{V}O_2$). Consequently, our results are applicable only to humans at rest.

METHODS

With approval of our institutional review board and with informed consent, we studied 11 patients before a surgical procedure with an anticipated blood loss of 2 L or more and 21 paid volunteers not undergoing surgery. Data from patients were collected before anesthesia and surgery. All volunteers and patients were without cardiovascular, pulmonary, or hepatic disease; did not smoke; and were not taking any drugs with cardiovascular actions.

Peripheral venous, radial arterial, and flow-directed pulmonary arterial (via the right internal jugular vein; Baxter Healthcare, Glendale, Calif) cannulas were inserted into each subject using local anesthesia. In 18 subjects an intravenous infusion of propofol (50-150 micrograms per kilogram per minute [$\mu g \cdot kg^{-1} \cdot min^{-1}$]) provided mild sedation during the introduction of the pulmonary artery cannula. Following insertion of the cannulas, subjects

rested for 30 minutes prior to measurement of variables. Intra-arterial, central venous, pulmonary arterial, and pulmonary capillary wedge pressures and heart rate were measured. Cardiac output (duplicate or triplicate if duplicates differed by more than 10%, by thermodilution; A/S3 Datex Medical Instrumentation, Tewksbury, Mass) was recorded before removal of any blood, and 5 to 10 minutes after isovolemic removal of each 450 to 900 mL of blood into collection bags (CPDA-1 collection bags, Baxter Healthcare Corp, Deerfield, Ill). Removal of each 450 mL of blood took approximately 10 minutes. Isovolemia was maintained by intravenous infusion of 5% human serum albumin (Baxter Healthcare, Glendale, Calif) and/or the subject's own platelet-rich plasma (after separation from the red blood cells of the removed blood). These were infused simultaneously with blood removal, in quantities approximately equal to that of the removed blood, to maintain constant central venous and pulmonary capillary wedge pressures. At the time of cardiovascular measurements, arterial and mixed venous blood was sampled for measurement of pH, oxygen content, and oxyhemoglobin saturation (OSM3 Hemoximeter, Radiometer, Copenhagen, Denmark) and arterial lactate concentration (Yellow Springs Instrument Co, YSI No. 2700, Yellow Springs, Ohio). Stroke volume index, systemic vascular resistance index, $\dot{T}O_2$, and $\dot{V}O_2$ were calculated by standard formulas. The subjects' pulmonary artery temperature was maintained at 37°C by body surface warming with heated air and by warming the infused fluids. The electrocardiogram (ECG; 5-lead in all subjects) was monitored and a 3-channel Holter ECG in 21 of the 32 subjects (3 patients and 18 volunteers) (Del Mar model 459, Del Mar Avionics, Irvine, Calif) was recorded continuously from 1 hour before through the 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, 3 bipolar leads—CC5, modified CM5, and ML—were used.[5] 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 (eg, 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 and Hb concentration. An ischemic episode was defined as a reversible ST-segment shift from baseline of 0.1 mV or greater depression at J + 60 msec, or 0.2 mV or greater elevation at the J point lasting for at least 1 minute. The time after the J point chosen to measure ST-segment depression was adjusted to exclude T wave during tachycardia.

Table 1.—Demographic Data (N=32)*

	All	Patients	Volunteers
Age, y	27 (19-69)	50 (35-69)	23 (19-33)†
Body surface area, m^2	1.85 (1.47-2.22)	2.01 (1.59-2.22)	1.80 (1.47-2.10)†
Male/female	16/16	8/3	8/13
Initial hemoglobin concentration, g/L	124±2	121±4	126±2

*Data are median (range).
†$P<.05$ vs patients.

The relationships of measured and calculated variables to Hb concentration were assessed by linear regression with repeated measures (JMP 3.1, SAS Institute, Cary, NC). To test for nonlinearity of the relationship of each variable to Hb concentration, we added a polynomial equation to the linear equation and retested the relationship. If the fit was not improved (interaction term, $P>.05$), a linear relationship was accepted.

The relationship between $\dot{T}O_2$ and Hb concentration was not linear. To find the Hb concentration at which $\dot{T}O_2$ began to decrease, we analyzed the relationship between $\dot{T}O_2$ and Hb concentration with a simultaneous fit of 2 linear regressions, using a population approach.[6] The relationship between $\dot{T}O_2$ and Hb concentration typically had 2 linear components: with Hb less than the inflection value (Hb_i), there was a steep relationship between Hb and $\dot{T}O_2$; with Hb larger than Hb_i, the slope of the relationship between Hb and $\dot{T}O_2$ was shallow and either positive or negative. Our analysis therefore determined Hb_i, $\dot{T}O_2$ at Hb_i [$\dot{T}O_2(Hb_i)$], and the slope of each of the 2 linear portions (ie, above [slope($Hb \geq Hb_i$)] and below Hb_i[slope($Hb < Hb_i$)]). This was accomplished by simultaneous fitting of 2 linear regressions that intersected at Hb_i and the corresponding value for $\dot{T}O_2$. Because the number of measurements of $\dot{T}O_2$ for each individual ranged from 5 to 11, the number of values that could be used to fit each of the 2 linear regressions would be small. Therefore, we applied a method of analysis—mixed-effects modeling—in which data for all subjects are analyzed simultaneously, accounting for interindividual differences in such covariates as age and sex; the analysis accounts for the repeated-measures nature of the data (NONMEM with the NONMEM program, Version V, Level 1.0L4[7]). The model contained 4 parameters, each of which was estimated: Hb_i, $\dot{T}O_2(Hb_i)$, slope($Hb > Hb_i$), and slope ($Hb < Hb_i$). For the first 3 of these parameters, interindividual variability was assumed to be log-normally distributed. To permit the fourth parameter to be either positive or negative, interindividual variability was modeled as normally distributed. Residual error between observed and measured values for $\dot{T}O_2$ was assumed to have a constant variance (ie, measurement error in $\dot{T}O_2$ did not vary with Hb). After each population fit was complete, we used NONMEM's post hoc step to obtain Bayesian estimates of the parameters for each individual; these Bayesian estimates were plotted against each of age, weight, sex, and body surface area to assess whether these covariates influenced the parameters. Goodness of fit was assessed by inspection of the fit of the population and Bayesian regression lines to the data for each individual and by NONMEM's objective function, – 2 log likelihood. Initially, we tested a model in which the "typical" values of the 4 parameters were the same for all subjects. Bayesian estimates suggested that Hb_i varied with age. Permitting Hb_i to vary with age improved the fit. Bayesian estimates from this model suggested that Hb_i differed between men and women. Incorporating this into the model further improved the fit (both by visual inspection and by an improvement in NONMEM's objective function). Bayesian estimates now suggested that slope ($Hb < Hb_i$) varied with age. Permitting slope ($Hb < Hb_i$) to vary continuously with age did not improve the quality of the fit; however, permitting slope ($Hb < Hb_i$) to differ between those younger and those older than 30 years of age markedly improved the fit (again, both by visual inspection and by an improvement in NONMEM's objective function). Bayesian estimates from this model no longer suggested a relationship between the covariates and the parameters.

For illustrative purposes (Figures) and to quantify the response of each variable to the reduction in Hb concentration, data were grouped by Hb concentration increments of 10 g/L. To determine the influence of subject age and sex on the response to acute isovolemic anemia, we performed a 2-way repeated-measures analysis of variance. Unless otherwise specified, all data are reported as mean (SE). Statistical significance was accepted at $P \leq .05$.

RESULTS

Patients were older and of greater weight and body surface area than the volunteers; there was no difference in initial Hb concentration or sex proportion between the 2 groups (Table 1). The dura-

Table 2.—Response to Acute Isovolemic Anemia*

Variable	Hemoglobin Range 125-134 g/L (n=23)	45-54 g/L (n=28)
SVRI, dyne·s·cm^{-5}·m^2	2372 (541)	1001 (176)
HR, beats per minute	58 (11)	92 (12)
SVI, mL/m^2	52 (9)	62 (8)
CI, L/m^2	3.05 (0.69)	5.71 (0.87)
To_2, mL O_2·kg^{-1}·min^{-1}	13.5 (2.7)	10.7 (2.0)
S_vO_2, %	77.1 (3.3)	69.6 (5.6)
$\dot{V}O_2$, mL O_2·kg^{-1}·min^{-1}	3.01 (0.42)	3.42 (0.54)
Plasma lactate, mmol/L	0.77 (0.40)	0.62 (0.19)
Arterial blood pH	7.395 (0.016)	7.445 (0.025)
Base-excess, mEq/L	1.3 (1.5)	4.2 (2.2)
$\dot{V}O_2/To_2$	0.23 (0.03)	0.32 (0.04)

*Data are mean (SD). Group sizes are less than 32 because not all subjects had a hemoglobin concentration within the range described. The statistical results provided in the text refer to all data for all subjects: all variables shown in this table, except plasma lactate concentration, changed significantly with decreasing hemoglobin concentration. SVRI indicates systemic vascular resistance index; HR, heart rate; SVI, stroke volume index; CI, cardiac index; To_2, oxygen transport; S_vO_2, mixed venous oxyhemoglobin saturation; and $\dot{V}O_2$, oxygen consumption.

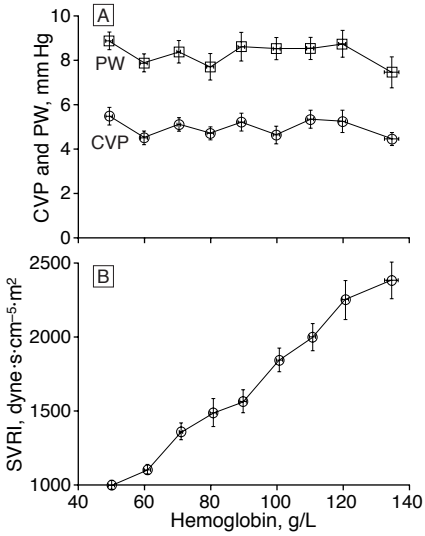

Figure 1.—A, Right heart (central venous pressure [CVP] and left heart (pulmonary capillary wedge pressure [PW]) did not change (P>.05) with acute isovolemic anemia. Data are gathered into groups by hemoglobin increments of 10 g/L and represented as mean (SE) (N=32). B, Acute isovolemic reduction of hemoglobin concentration to 50 g/L decreased systemic vascular resistance index (SVRI; P<.001) by 58%. Data are gathered into groups by hemoglobin increments of 10 g/L and represented as mean (SE) (N=32).

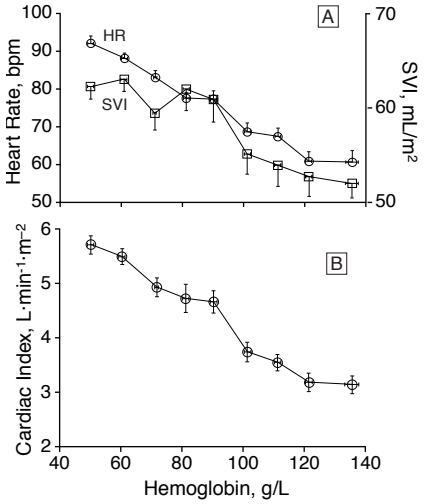

Figure 2.—Acute isovolemic reduction of hemoglobin concentration to 50 g/L increased heart rate (HR) (A; P<.001), stroke volume index (SVI) (A; P<.001), and cardiac index (B; P<.001). Data are gathered into groups by hemoglobin increments of 10 g/L and represented as mean (SE) (N=32); bpm indicates beats per minute.

tion of experimentation was 2.4 (0.1) hours (mean [SD]) and the volume of albumin plus plasma infused was 1.1 (0.1) times the volume of blood removed.

Right- and left-heart filling pressures (central venous and pulmonary capillary wedge pressures) did not change with acute severe isovolemic anemia (Figure 1, P>.05). Decrease of Hb concentration from 131 (2) g/L (mean [SE]) to 50 (1) g/L decreased systemic vascular resistance index by 58% (Table 2, Figure 1, P<.001), increased heart rate (Table 2, Figure 2, P<.001), stroke volume index (Table 2, Figure 2, P<.001), and cardiac index (Table 2, Figure 2, P<.001). The relationship of heart rate to Hb concentration for each subject is depicted in Figure 3.

The increase in cardiac index compensated for the decreased arterial oxygen content, maintaining To_2 until Hb concentration decreased to a value (Hb_i) that depended on age and was determined by population analysis. At Hb concentrations above Hb_i the slope of the relationship was × 0.669 milliliters of oxygen per kilogram per minute (mL O_2·kg^{-1}·min^{-1})/grams of Hb per liter (gHb/L). The optimal model found Hb_i for males = 71.4 + 0.154·age(years) g/L and for females = 49.9 + 0.154·age(years) g/L. Below Hb_i the relationship was influenced by age: at age younger than 30 years, slope = 12.3 (mL O_2·kg^{-1}·min^{-1})/(gHb/L); at age 30 years or older, slope = 4.06 (mL O_2·kg^{-1}·min^{-1})/(gHb/L). The To_2 at Hb_i was 13.4 mL O_2·kg^{-1}·min^{-1}.

Thereafter, compensation was incomplete, resulting in decreased To_2 (Figure 4, P<.001), and decreased mixed venous oxyhemoglobin saturation (Figure 4, P<.001).

Although To_2 decreased at the lowest Hb concentrations, $\dot{V}O_2$ increased slightly (Table 2, Figure 5, P<.001). Plasma lactate concentration did not change (Table 2, Figure 6, P=.09); arterial blood pH and base excess increased slightly (Table 2, P<.001). There was no relationship between $\dot{V}O_2$ and To_2 in any subject.

No ST changes were observed in the online monitored ECG. Eighteen of the 21 Holter tapes could be analyzed completely. There were 2 brief episodes that met the criteria for significant ST changes. One episode was for 10 minutes in a 27-year-old woman when her Hb concentration was 62 g/L when she was sitting to urinate. Her To_2 and consumption at that Hb concentration were normal: 16.0 and 3.9 mL O_2·kg^{-1}·min^{-1}, respectively, and she had no cardiac symptoms. The ST changes resolved spontaneously with reclining. Further reduction of her Hb concentration to 49 g/L with a concomitant reduction of To_2, but not $\dot{V}O_2$, did not produce ST changes. The other episode was a 0.11-mV ST depression in a 25-year-old woman when her Hb concentration was 46 to 53 g/L. Her To_2 at that time was 10.9 to 12.1 mL O_2·kg^{-1}·min^{-1} and $\dot{V}O_2$ was 3.9 to 4.0 mL O_2·kg^{-1}·min^{-1}, unchanged from her baseline. These changes resolved at an Hb concentration of 46 g/L when her heart rate slowed from 110 to 89 beats per minute (with administration of esmolol, administered after the data reported here were collected, as part of a separate protocol in a subset of these subjects). The decrease in heart rate reduced To_2 to 8.1 mL O_2·kg^{-1}·min^{-1}, with a $\dot{V}O_2$ of 3.6 mL O_2·kg^{-1}·min^{-1}. At the lowest Hb concentrations many subjects reported fatigue but no other symptoms referable to decreased To_2 or hypoxia.

Sex had no influence except for women having a lesser stroke volume index (P=.017) (and a lower Hb concentration at which To_2 decreased; see above). Older subject age was associated with a higher mean arterial blood pressure (P=.007) (and a higher Hb concentration at which To_2 decreased; see above). However, since our patients were older than the volunteers, it was not possible to determine whether these effects related to age or population.

COMMENT

The major finding of this study is that acute reduction of blood Hb concentration to 50 g/L in conscious healthy resting humans does not result in detectable inadequate systemic To_2. The systemic markers we used to detect consequences of inadequate To_2 ($\dot{V}O_2$ and plasma lactate concentration) did not demonstrate inadequate To_2 with decreased Hb concentration. The lack of significantly increased plasma lactate in any of the 32 subjects indicates, with a 95% assurance, that acute reduction of Hb concentration to 50 g/L would not produce lactic acidemia in more than 9% of the population.[8] It would appear that the ST findings in the sitting subject were likely related to body position. We were unable to determine if the 0.11-mV ST change in the second subject was related to heart rate per se or to heart rate–induced myocardial ischemia. Based on data from acutely anemic conscious

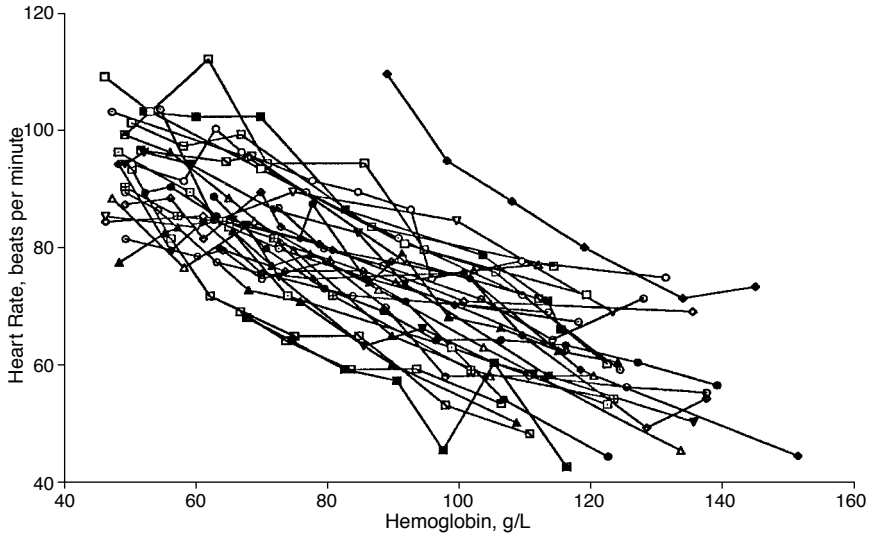

Figure 3.—Heart rate response to acute isovolemic anemia in all subjects.

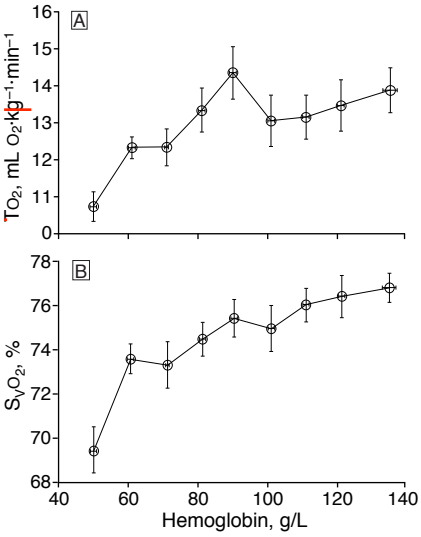

Figure 4.—Acute isovolemic reduction of hemoglobin concentration to 50 g/L decreased oxygen transport rate (DO_2) (A; $P<.001$) and mixed venous oxyhemoglobin saturation (S_vO_2)(B; $P<.001$). Data are gathered into groups by hemoglobin increments of 10 g/L and represented as mean (SE) (N=32).

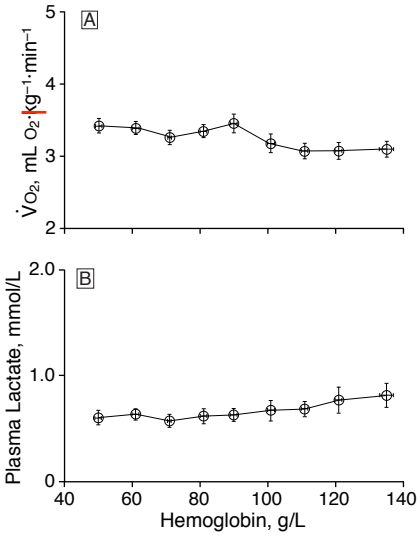

Figure 5.—Acute isovolemic reduction of hemoglobin concentration to 50 g/L increased oxygen consumption ($\dot{V}O_2$) (A; $P<.001$) but did not change plasma lactate concentration (B;$P=.09$). Data are gathered into groups by hemoglobin increments of 10 g/L and represented as mean (SE) (N=32).

dogs, reducing heart rate from 110 to 89 beats per minute would decrease myocardial $\dot{V}O_2$ by approximately 22%.[9,10] If we accept an incidence of 1 in 18, ST changes would not be expected to occur (with 95% assurance) in more than 16% of the population (incidence + 2 times the SE of the proportion). With an incidence of zero in 18, ST changes, with 95% assurance, would not be expected to occur in more than 15% of the population.[8]

Our data are consistent with those obtained in conscious dogs[10] and baboons.[11] Acute reduction of hematocrit to 0.10 to 0.15 in conscious resting dogs and to 0.15 in conscious restrained baboons produced cardiovascular effects similar to those we observed in humans (decreased systemic vascular resistance; increased heart rate, stroke volume [dogs, but not baboons], and cardiac index), without change in $\dot{V}O_2$.[10,11] The decreased systemic vascular resistance is, in part, related to the decreased blood viscosity[12] and, in part, to increased cross-sectional area of the vascular bed. We accomplished intravascular dilution with albumin and plasma so that altered viscosity in our subjects resulted solely from the decreased red cell concentration.

In our subjects, increased heart rate contributed approximately 75% and increased stroke volume approximately 25% of the increased cardiac output. These values are similar to those of 69% and 31%, respectively, in acutely anemic conscious dogs.[10] Inadequate DO_2 results in an inability to sustain $\dot{V}O_2$. Our subjects actually increased their $\dot{V}O_2$ by approximately 14% at an Hb concentration of 50 g/L. This is likely due to the increased heart rate and/or sympathetic stimulation. If the relationship between myocardial $\dot{V}O_2$ and heart rate during acute anemia is similar to that of the dog,[9,10] increased myocardial $\dot{V}O_2$ accounted for approximately one fourth of our measured increased systemic $\dot{V}O_2$. Our result is consistent with the finding by Cain[13] of a small increase in the $\dot{V}O_2$ of anesthetized dogs, at a hematocrit just above that which decreased $\dot{V}O_2$ (hematocrit approximately 0.10). We found that DO_2 was maintained at Hb concentrations of at least 65 g/L for a 20-year-old woman and 92 g/L for a 20-year-old man. These values increased with increasing subject age. Our finding differs from that in conscious dogs of a linear decrease in DO_2 with decreasing Hb concentration.[10] The decreased DO_2, however, does not imply inadequate delivery of oxygen to tissues.

Cain defined the "critical" DO_2 as that which is inadequate to prevent a decrease in $\dot{V}O_2$.[13] The critical systemic value varies among species: approximately 10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in anesthetized dogs with mechanically ventilated lungs,[13] and 23 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in anesthetized rats.[14] In anesthetized dogs, systemic DO_2 becomes critical at an Hb concentration of 30 to 50 g/L.[15] In dogs, the critical myocardial DO_2 occurs at approximately the same Hb concentration as does the systemic DO_2.[16] This adds support to our interpretation that the ST change that occurred in the one volunteer, in the absence of evidence of inadequate systemic DO_2, was likely related to heart rate per se and not myocardial ischemia. Reducing hematocrit to 0.17 in conscious dogs did not decrease splanchnic $\dot{V}O_2$ or hepatic function,[17] and reducing hematocrit to 0.15 in anesthetized pigs did not alter systemic or hepatic $\dot{V}O_2$ or hepatic lactate uptake.[18] Oxygen delivery of 16 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ at a hematocrit of 0.10 to 0.15 in conscious resting dogs did not produce evidence of inadequate DO_2,[10] nor did delivery of 11 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ at a hematocrit of 0.15 in conscious restrained baboons.[11]

The "critical" value of DO_2 in humans has not been determined. An evaluation of the reports of clinical experiences with Jehovah's Witnesses who refused transfusion suggested that an Hb concentration of 50 g/L or greater is not associated with increased mortality, but could not assess the level of critical DO_2.[19] van

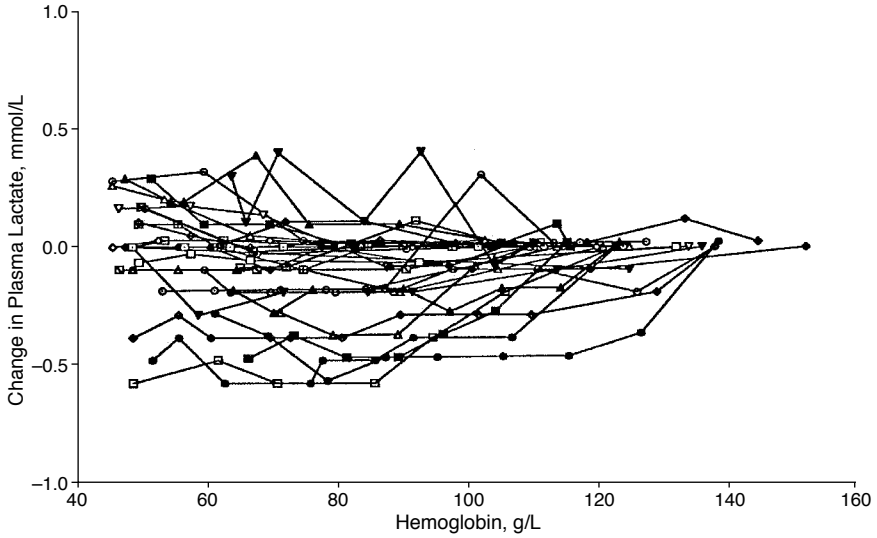

Figure 6.—Change in plasma lactate concentration in all subjects.

Woerkens et al[20] reported a critical value of 4.9 mL O_2·kg^{-1}·min^{-1} in an anesthetized 84-year-old man with pharmacologically induced neuromuscular blockade and mechanically ventilated lungs. The critical value for Hb or $T\dot{V}O_2$ has not been determined in any conscious species at rest. Reducing $\dot{V}O_2$ by anesthesia, neuromuscular blockade, and mechanical ventilation of the lungs would likely decrease the critical value for $T\dot{V}O_2$ below that of the normal conscious state. Anesthetics decrease systemic $\dot{V}O_2$, myocardial contractility, and thereby myocardial $\dot{V}O_2$.[21] Anesthetic-induced cortical electrical silence reduces cerebral $\dot{V}O_2$ by approximately half.[22] Neuromuscular blockade reduces muscle $\dot{V}O_2$ by eliminating movement. Mechanical ventilation of the lungs decreases the $\dot{V}O_2$ of the muscles of respiration, but also decreases venous return, and thereby cardiac output. Additionally, many anesthetized humans are mildly hypothermic, further decreasing $\dot{V}O_2$. Most anesthetics also decrease cardiac output.[21] Thus, data from anesthetized animals or humans cannot be extrapolated to the conscious state because of alteration of both $\dot{V}O_2$ and $T\dot{V}O_2$. Similarly, our data cannot be extrapolated to conditions other than rest. In dogs, exercise decreases the ability to compensate for acute anemia: systemic $\dot{V}O_2$ decreases[10] and the coronary arteries dilate maximally[9] at higher Hb concentrations than during rest.

Our effort to determine the critical level of $T\dot{V}O_2$ in conscious resting humans failed. Mean $T\dot{V}O_2$ was 10.7 (0.4) mL O_2·kg^{-1}·min^{-1} at an Hb level of 50 (1) g/L. Fourteen of our 32 subjects had $T\dot{V}O_2$ of less than 10 mL O_2·kg^{-1}·min^{-1}; the lowest $T\dot{V}O_2$ achieved was 6.5 mL O_2·kg^{-1}·min^{-1}. Nevertheless, we did not find evidence of systemic acidosis in any subject. The slight increases of arterial blood pH and base excess were likely a result of the infused citrate anticoagulant (contained within the plasma). The electrocardiographic ST changes in 1 subject could have been related to heart rate or could have represented transient myocardial ischemia. Although we used a standard measure of myocardial ischemia that provides continuous measurement and printed availability for validation,[23] it remains possible that some episodes of ischemia might not have been detected.[24]

"Guidelines," "standards," and "practice parameters" have suggested that patients without cardiovascular or pulmonary disease need not be given red blood cell transfusion unless their Hb concentration is less than 70 g/L[1] or 60 g/L.[3] The development of these documents and the advice they contain has been hampered by limited human data on which the authors and committees could rely. Our data support these recommendations and suggest that in healthy resting patients not taking drugs with cardiovascular actions, even lower Hb concentrations are tolerated without apparent adverse metabolic sequelae. We were unable to determine the critical Hb value in our healthy subjects, and thus cannot provide a definitive Hb concentration likely to require red blood cell transfusion. However, the human critical value for $T\dot{V}O_2$ is less than 10 mL O_2·kg^{-1}·min^{-1}, a level reached in normal humans at an Hb concentration of 50 g/L. Our subjects were studied supine, at rest. Thus, our results should not be extrapolated to circumstances of increased $\dot{V}O_2$ (eg, activity), decreased ability to increase cardiac output (eg, cardiac disease, medications), or decreased ability to increase specific organ or tissue blood flow (eg, arterial stenosis).

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The caring physician has a major responsibility in educating the patient as to the realistic potential for survival. It is not appropriate to tell patients how many weeks or months they have to live. It is reasonable to stress the incurability of the disease, the lack of specific anticancer therapy or even suitable clinical trials, and the plans for supportive care to attain a desired quality of life in the process of dying.

Terminal cancer should be excluded from physician language and scientific publications, just as the American Cancer Society has urged exclusion of the terms *victim* and *terminal* from its programs and publications (Harman Eyre, MD, American Cancer Society, written communication, June 18, 1998).

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In Reply.—Dr Costantini-Ferrando and colleagues confirm our findings that patients with cancer tend to overestimate their prognoses. More important, they shed light on how this failure of communication actually may be contributing to patients' suffering at the end of life. We found that patients' perceptions of their prognoses were associated with a preference for life-extending therapy, which, in turn, was associated with higher rates of adverse events in the last months of life. Costantini-Ferrando and colleagues identify a possible mediator for this effect, namely, that patients' perceptions of their prognoses may be driving their willingness and desire to even discuss palliative care. Their observation that avoidant thinking also was associated with an unwillingness to discuss palliative care decisions underscores how difficult it may be to successfully intervene in this dynamic. Our finding that patients who simply understood that there was at least a 10% probability that they might not survive 6 months had substantially different treatment preferences suggests that these avoidant tendencies need not be fully overcome, however, to help patients make treatment decisions that are consistent with their underlying values.

Dr Kennedy's insightful comments remind us of the importance of careful and compassionate choice of language in discussions with patients regarding their prognoses. However, our data do not support his contention that physicians are unable to prognosticate for individual patients, and therefore that discussions of life expectancy, even in general terms, are not appropriate.

Our receiver operating characteristic curve analysis indicated that physicians in our cohort were quite accurate in estimating individual patients' prognoses. In particular, physicians were able to discriminate between patients who ultimately did and did not survive for 6 months. Our findings that physicians are in a position to provide patients with accurate information about prognosis, and that patients who understand this information are less likely to experience adverse events, suggest that withholding such prognostic information from patients, even if it is done with the most altruistic motives, may not be the most compassionate approach to care at the end of life.

As we move toward an evidence-based approach to defining optimal end-of-life care, the need for further research on how to elicit, understand, and honor patients' preferences, regarding not only treatment choices, but also styles and modes of communication about prognosis, is clearly critical.

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In Reply.—I agree with Dr Kennedy that the term *terminal* seems impersonal, but it is truthful. I do not use terminal unless a patient asks me specifically, but I have always preferred to say, "You have a disease that cannot be cured with medicines." However, it is important to emphasize that data for populations do apply to individuals. If 95 of 100 patients with advanced pancreatic cancer will be dead within 1 year, then the patient should know that. If all that the patient hears is "You have pancreatic cancer" and "Some people do well, after all, not everyone is the same," they have not been given decent information.

I agree with Dr Costantini-Ferrando and colleagues that "one-size-fits-all" discussion does not fit all. But I have heard too often "They never brought it up" or "I thought it would disturb them" as reasons that a patient's incurable disease never was discussed. If physicians try to tailor everything to personality style, I suspect we would err quite frequently, and this approach might give yet another excuse to avoid the issue. The only way to know what patients want is to ask them.

The most important part of the discussion about dying is to start one, just as the biggest hurdle of going into a dying person's room is to enter the room and sit. The discussion can then start, "What would you like to know about your illness?" and lead to the finer points about prognosis, what can be done, and what cannot be done.

Granted, none of this is pleasant for physicians or for patients. The most difficult aspects of cancer care are those transition points when active therapy can no longer help, and clinicians must help patients to switch from "I could be in that 5 in 100 group" to planning for end of life. After all, planning for end of life if the patient is in the 95 of 100 group does not diminish his or her chances of living longer. Until physicians admit how difficult it is and learn these important skills and have societal expectations that not all diseases can be cured, patients and physicians will continue to fight battles that cannot be won and are lost with too much suffering.

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CORRECTION

Error in Table.—An error occurred in the Clinical Investigation entitled "Human Cardiovascular and Metabolic Response to Acute, Severe Isovolemic Anemia" published in the January 21, 1998, issue of THE JOURNAL (1998;279:217-221). On page 218, in Table 1, the median age range under "Patients" should have read "(35-69)" [not (35-39)].