High Oxygen Partial Pressure Decreases Anemia-induced Heart Rate Increase Equivalent to Transfusion

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ABSTRACT

Background: Anemia is associated with morbidity and mortality and frequently leads to transfusion of erythrocytes. The authors sought to directly compare the effect of high inspired oxygen fraction *versus* transfusion of erythrocytes on the anemia-induced increased heart rate (HR) in humans undergoing experimental acute isovolemic anemia.

Methods: The authors combined HR data from healthy subjects undergoing experimental isovolemic anemia in seven studies performed by the group. HR changes associated with breathing 100% oxygen by nonrebreathing facemask *versus* transfusion of erythrocytes at their nadir hemoglobin concentration of 5 g/dl were examined. Data were analyzed using a mixed-effects model.

Results: HR had an inverse linear relationship to hemoglobin concentration with a mean increase of 3.9 beats per min per gram of hemoglobin (beats/min/g hemoglobin) decrease (95% CI, 3.7–4.1 beats/min/g hemoglobin), $P < 0.0001$. Return of autologous erythrocytes significantly decreased

What We Already Know about This Topic

- Anemia is an independent predictor of increased morbidity in surgical patients and compensatory tachycardia that occurs during anemia may contribute to increased risk, particularly in patients with cardiovascular disease

What This Article Tells Us That Is New

- Healthy subjects breathing oxygen during severe anemia demonstrated decreases in heart rate by an amount equivalent to that of increasing hemoglobin concentration by approximately 3 g/dl
- Supplemental oxygen could be a temporizing measure before transfusion of erythrocytes is initiated

HR by 5.3 beats/min/g hemoglobin (95% CI, 3.8–6.8 beats/min/g hemoglobin) increase, $P < 0.0001$. HR at nadir hemoglobin of 5.6 g/dl (95% CI, 5.5–5.7 g/dl) when breathing air (91.4 beats/min; 95% CI, 87.6–95.2 beats/min) was reduced by breathing 100% oxygen (83.0 beats/min; 95% CI, 79.0–87.0 beats/min), $P < 0.0001$. The HR at hemoglobin 5.6 g/dl when breathing oxygen was equivalent to the HR at hemoglobin 8.9 g/dl when breathing air.

Conclusions: High arterial oxygen partial pressure reverses the heart rate response to anemia, probably because of its usability rather than its effect on total oxygen content. The benefit of high arterial oxygen partial pressure has significant potential clinical implications for the acute treatment of anemia and results of transfusion trials.

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ANEMIA is associated with many comorbidities, such as renal and cardiac disease, as well as with numerous adverse outcomes, including mortality. A comprehensive review of reported cases and series of untransfused Jehovah's Witness patients found no mortality when the hemoglobin concentration exceeded 5 g/dl, but a 44% mortality when the hemoglobin concentration was less than 5 g/dl.[1] Database analyses of surgical patients who refused transfusion found increased mortality with decreased hemoglobin concentrations[2,3] and that the presence of cardiovascular disease substantially increased that risk.[2] Two more recent retrospective analyses of large databases found that anemia was indepen-

Table 1. Summary of Studies

Study	No. of Subjects	Sex (F/M)	Return	O_2	Slope (95% CI)
Weiskopf et al.[6]	32	16/16	No	No	− 4.48 (− 4.17 to − 4.79)
Hopf et al.[34]	14	10/4	No	No	− 3.79 (− 3.30 to − 4.27)
Weiskopf et al.[35]	11	5/17	Yes	No	− 3.80 (− 3.25 to − 4.35)
Weiskopf et al.[12]	30	20/10	No	Yes	− 3.36 (− 2.99 to − 3.74)
Weiskopf et al.[36]	8	5/3	No	No	− 3.61 (− 2.76 to − 4.46)
Weiskopf et al.[13]	14	10/4	No	Yes	− 3.74 (− 2.99 to − 4.50)
Weiskopf et al.[11]	9	6/3	Yes	No	− 3.92 (− 3.41 to − 4.42)
Totals	129	72/57	—	—	—

Return refers to data available on re-transfusion of autologous blood; O_2 refers to data taken on and off oxygen by nonrebreather; in some cases we report more subjects than in the original manuscript because of incomplete dataset for the primary outcome.

dently associated with adverse outcomes in surgical patients, even when controlling for comorbidities.[4,5] The reasons for worse outcomes are not known, but likely include inadequate oxygenation of tissues and stresses related to physiologic compensation for anemia. Elevation of heart rate is an important compensatory mechanism for maintaining oxygen delivery during anemia.[6] However, tachycardia has adverse consequences for patients with coronary artery disease. It is associated with myocardial ischemia during the postoperative period in those patients with or at risk for coronary artery disease,[7] and postoperative ischemia is associated with adverse outcomes in those patients.[8]

Erythrocytes are often transfused to reduce or prevent cardiac ischemia associated with the tachycardia of anemia, but the benefits may not outweigh the risks.[9] We have previously shown that heart rate increases linearly as hemoglobin decreases during isovolemic anemia in awake, unsedated humans,[10] and that transfusion of erythrocytes or breathing oxygen reverses the signs and symptoms of acute anemia.[11–13] There are few studies examining oxygen reversal of the effects of anemia, and none comparing a quantitative physiologic effect of oxygen with that of erythrocyte transfusion. We report here the effect of transfusion, and that of oxygen, on reversing the increased heart rate due to anemia, using the data we have accumulated in several studies of acute isovolemic anemia in more than 100 awake, unmedicated healthy people.

Materials and Methods

We combined data from six published studies over 8 yr during which we produced acute isovolemic anemia (table 1). Data from some published studies were subsets of the studies in table 1 and are not listed separately[14–16]; however, all studied subjects are included in our analyses. All studies were performed with approval of the Institutional Review Board at the University of California, San Francisco and informed consent of every subject. All subjects were healthy volunteers except for 11 healthy patients about to undergo major orthopedic surgery. Subjects and patients were free of cardiovascular, pulmonary, renal, and hepatic disease as determined by history, physical examination, and laboratory analyses.

The method for producing isovolemic anemia has been previously reported.[6] Briefly, whole blood was removed from nonanesthetized awake subjects or patients through an indwelling large-bore peripheral intravenous cannula into CPDA-1 collection bags (Baxter Healthcare Corporation, Deerfield, IL). We infused warmed 5% albumin or the subject's autologous platelet-rich plasma, or both, simultaneously through a peripheral intravenous cannula in the opposite arm, in quantities sufficient to maintain isovolemia.[6] At least 10 min were allowed for removal of each unit of blood. Heart rate was recorded 5–10 min after removal of blood to ensure physiologic stabilization.

At least two units of packed erythrocytes were reinfused at the end of each study. Remaining erythrocytes were infused slowly overnight, but without recording heart rate data. Two studies included a total of 36 subjects randomly allocated to breathe air or 100% oxygen through a nonrebreathing facemask at the nadir hemoglobin concentration. All available heart rate and hemoglobin data are included in the analyses reported here.

Statistics

Using a mixed-effects linear regression model, we assessed the effects of breathing oxygen during anemia by examining the relationship between heart rate (HR) and hemoglobin concentration when each subject breathed either air or oxygen (order randomly allocated). This is a repeated-measures model that allows each person to have an individual fitted line with its own slope and intercept. To examine whether the relationship between HR and hemoglobin was linear for the entire range of data, the linear model was applied to the dataset using several upper cutoff values of hemoglobin. To test for linearity, a quadratic term (hemoglobin[2]) was added to the model and tested for statistical significance. The effect of sex on the slope of the relationship was also examined in the model by testing the interaction term of sex and hemoglobin. The mixed-effects model was also performed separately for male and female individuals, and the 95% confidence limits for the slopes computed. A random effect for the different studies was also added in the model. Thus, the complete model included a repeated measures analysis, with
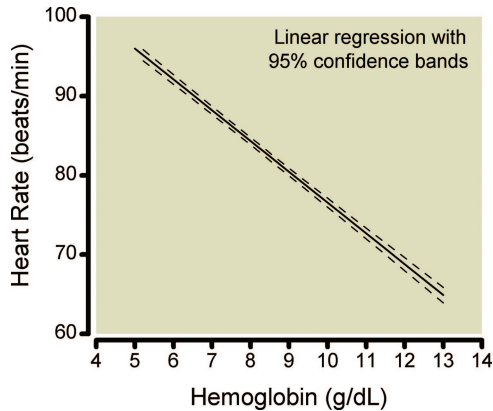
Fig. 1. Linear regression of heart rate and hemoglobin for 129 individuals during isovolemic hemodilution. *Dashed lines* represent the 95% confidence bands derived from the mixed-effects (repeated measures) model.
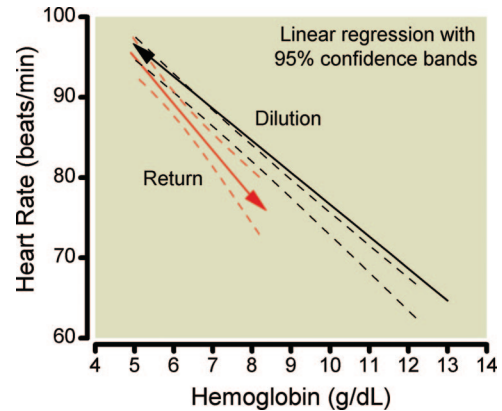

Fig. 2. Linear regressions for the 33 individuals who had at least two hemoglobin values after transfusion. The *solid line* represents the regression for these subjects during isovolemic hemodilution, with 95% confidence bands. The *dashed line* represents the regression for the same individuals during transfusion of their autologous erythrocytes, with 95% confidence bands. Heart rate during dilution differed significantly from return of erythrocytes, $P = 0.009$. Isovolemia was not maintained with return of erythrocytes.

random effects of study identity and of subjects nested within sex, and the interaction of sex and hemoglobin.

The basic mixed effects model was then expanded to include data from the reinfusion of autologous erythrocytes for those subjects for whom we had data both during dilution and return of autologous erythrocytes, or for whom we had data when they breathed oxygen in addition to room air at their nadir hemoglobin concentration. The heart rate at the nadir hemoglobin while subjects breathed air was compared by paired Student t test with their heart rate when they breathed oxygen.

Data were analyzed using JMP 7.0 (SAS Institute, Cary, NC). Data are reported as mean (95% CI). $P < 0.05$ was considered statistically significant.

Results

Data from 129 subjects (72 women and 57 men) were combined. HR had an inverse linear relationship to hemoglobin concentration ($P < 0.0001$, fig. 1), with an increase of 3.9 (95% CI, 3.7–4.1) beats/min/g hemoglobin concentration decrease.

Return of Erythrocytes

Data after transfusion of autologous erythrocytes were available for 61 subjects, of whom 33 subjects had at least two data points during return of blood for both HR and hemoglobin. These included nine subjects who were studied on two separate days comparing the effects of fresh and stored blood. Data from the 2 days were not statistically different and were pooled.

HR differed significantly between hemodilution and return of erythrocytes ($P = 0.009$). Return of autologous erythrocytes significantly decreased HR by 5.3 beats/min/g hemoglobin increase (95% CI, 3.8–6.8 beats/min/g hemoglobin) ($P < 0.0001$, fig. 2). This slope was not different ($P = 0.09$) from the slope for these same 33 individuals during hemodilution, 4.0 beats/min/g hemoglobin (95%

CI, 3.6–4.4 beats/min/g hemoglobin). (In the mixed-effects model, the "direction" [return *vs.* dilution] was statistically significant, but the interaction term between hemoglobin and direction was not statistically significant.)

Effect of Oxygen

Thirty-six subjects (25 women and 11 men) had heart rate data at nadir hemoglobin concentrations when breathing both air and oxygen (doubled-blinded and order randomly allocated). The HR at nadir hemoglobin of 5.6 g/dl (95% CI, 5.5–5.7 g/dl) when breathing air was 91.4 beats/min (95% CI, 87.5–95.3 beats/min). This differed from the HR when breathing oxygen at the same hemoglobin concentration, 83.0 beats/min (95% CI, 78.8–87.2 beats/min) ($P < 0.0001$). In 29 subjects with heart rate data at the nadir hemoglobin concentration (while breathing air) before beginning the randomized air or oxygen breathing, the heart rate was 96.3 beats/min (95% CI, 92.0–100.5 beats/min), which was significantly different from corresponding air value, 92.3 beats/min (95% CI, 87.3–97.3 beats/min), $P = 0.0063$. The HR when breathing oxygen differed significantly from the 95% confidence limits of the regression during hemodilution (while breathing air) for these 36 subjects (effect of oxygen, $P < 0.0001$; fig. 3). The HR when subjects breathed oxygen at hemoglobin 5.6 g/dl was approximately equivalent to that when breathing air at hemoglobin 8.9 g/dl (fig. 3). The effect of oxygen was confirmed in the complete mixed-effects regression model ($P < 0.0001$).

Linearity and Sex During Hemodilution

The relationship between heart rate and hemoglobin fit a linear model. A statistically significant quadratic term could only be found in male subjects when restricting the analysis
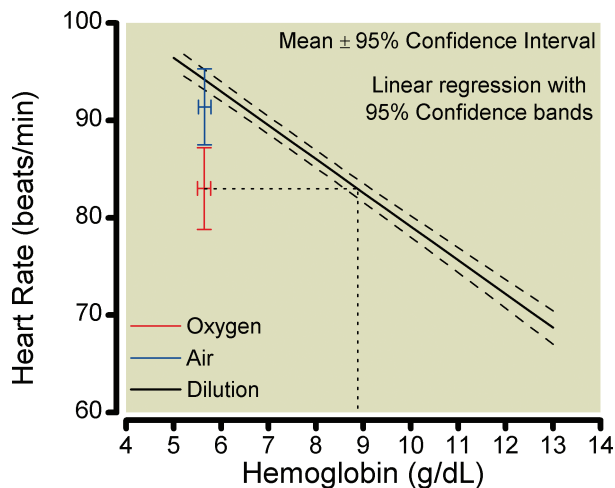
Fig. 3. Linear regression during isovolemic hemodilution for the 36 individuals with complete data when breathing oxygen and air (random assignment) at the nadir hemoglobin with 95% confidence bands. The *blue marker* indicates heart rate (mean ± 95% CI) breathing air; the *red marker* indicates heart rate breathing oxygen. The *dashed line* from the diamond projected to the dilution regression indicates the hemoglobin at a heart rate equivalent to that breathing oxygen at a hemoglobin concentration of 5.6 g/dl.

to hemoglobin ≤12 g/dL and hemoglobin ≤13 g/dl. The linear relationship between heart rate and hemoglobin concentration differed significantly ($P < 0.0001$) between men and women. In a comparable range of hemoglobin values (4–12 g/dl), HR in men increased 3.4 beats/min/g hemoglobin (95% CI, 3.0–3.8 beats/min/g hemoglobin) whereas HR in women increased by 4.6 beats/min/g hemoglobin (95% CI, 4.2–5.0 beats/min/g hemoglobin).

Discussion

Our main finding is that breathing oxygen during severe anemia reduces heart rate by an amount equivalent to the augmentation of hemoglobin concentration by approximately 3 g/dl. In addition, we have extended our previous finding of a linear relationship between HR and acute isovolemic anemia with heart rate increasing 4 beats/min/g hemoglobin decrease; and the relationship between HR and hemoglobin concentration is different between men and women.

The relationship between hemoglobin and HR was linear. Our previous analysis of this relationship[10] was confirmed with this extended dataset.

Women had a larger increase in HR in response to decreasing hemoglobin concentration than men. The predicted HR difference of 6 beats/min at a hemoglobin concentration of 5 g/dl is the equivalent to a hemoglobin difference of approximately 1.5 g/dl. Although this may not seem large, it is a difference that could affect choice of transfusion thresholds and the tolerance of profound anemia between men and women. We have shown previously that the oxygen delivery

decrease during profound anemia occurs later in women than in men.[6] The HR differences probably are an important component of this greater tolerance to profound anemia.

Reversal of the HR response by transfusion of erythrocytes was expected. We had found previously that there were no differences in the reversal of HR changes between fresh autologous blood and autologous blood stored for 21 days.[11] In the current analysis, there were small but statistically significant differences between the HR during hemodilution and the reinfusion of erythrocytes. Our experimental method provides for very good control of isovolemia during dilution, and we have shown that our physiologic measurements are not confounded by change in cardiac preload.[6] However, return of erythrocytes was not accomplished with maintenance of isovolemia: the transfusion of two units of erythrocytes likely expanded blood volume by approximately 7%. Therefore, the HR changes may have been affected not only by the increase in hemoglobin concentration, but also by this relatively modest increase in blood volume, and thus, it is not unexpected that the HR changes during transfusion differed slightly and were statistically significant from changes during isovolemic dilution. The differences are not clinically significant, were detected only by the use of a very sensitive statistical analysis, and were likely due to slight augmentation of blood volume, and thus, preload.

A high inspired oxygen fraction (F_{IO_2}) substantially reduced the increased heart rate produced by anemia. This finding is not consistent with the conventional wisdom that dissolved oxygen does not deliver a substantial quantity of oxygen. We noted this effect of high F_{IO_2} during previous studies[12,13] and sought to quantify its physiologic consequences here with greater accuracy, using data pooled from several studies, and to compare the effect with that of transfusion. Ideally, we would have data for supplemental oxygen and transfusion in the same subjects; we do not. However, the amount of data available to us retrospectively were substantial, and analysis of the complete dataset has produced valuable results. Our estimate that the HR changes from supplemental oxygen are equivalent to an increase of 3 g/dl of hemoglobin are based on comparing the HR while breathing oxygen to the HR during hemodilution while breathing air. Comparing the HR while breathing air (91.4 beats/min) to that while breathing oxygen (83.0 beats/min) at the nadir hemoglobin would produce an equivalent of 2 g/dl hemoglobin (fig. 3). The HR when breathing air, while within the 95% confidence estimates in figure 3, appears slightly lower than expected. HR data for 29 subjects immediately before the randomized air or oxygen treatment showed a significantly higher heart rate of 96 beats/min. A decreased HR response, or a prolonged effect of oxygen,[17] may have occurred in those subjects who received oxygen first; however, our inability to demonstrate an effect of the treatment order[12] argues against these possibilities.

The small amount of oxygen dissolved in plasma (0.0031 ml O_2/dl/mmHg) at normal arterial oxygen partial pressure
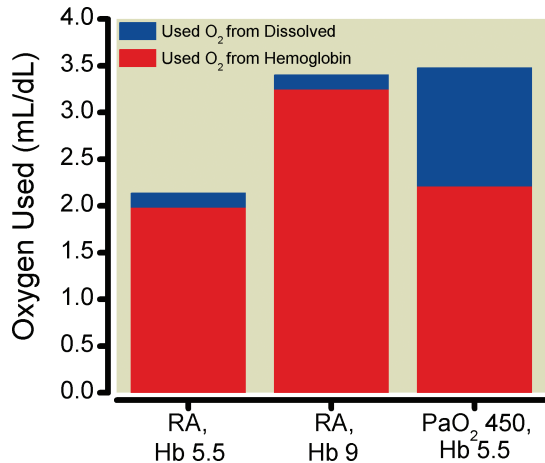
Fig. 4. Calculated data for the amount of oxygen (O_2) used by tissues that came from hemoglobin and dissolved sources: at hemoglobin 5.5 g/dl and a room air (RA) arterial oxygen partial pressure (Pa_{O_2}) = 90 mmHg (RA, hemoglobin 5.5), at hemoglobin 9.0 g/dl and RA, Pa_{O_2} = 90 mmHg (RA, hemoglobin 9), and at hemoglobin 5.5 g/dl and Pa_{O_2} = 450 mmHg (Pa_{O_2} 450, hemoglobin 5.5). Venous (tissue) P_{O_2} was 40 mmHg and venous oxygen saturation was 70% for the calculations.

(Pa_{O_2}) (approximately 0.3 ml/dl) is more substantial at high F_{IO_2}. However, mathematically, a Pa_{O_2} of 450 mmHg would be required to have an amount of dissolved oxygen equivalent to the 1.34 ml oxygen carried by 1 g of hemoglobin. This suggests that even high F_{IO_2} would not contribute a sufficient amount of dissolved oxygen to lower the heart rate by more than 4 beats/min in anemic subjects. With normoxia, even with anemia, only approximately 22% of the oxygen carried by hemoglobin is used when arterial blood at a Pa_{O_2} of 90 mmHg with an oxyhemoglobin saturation of 97% traverses to venous blood and a mixed-venous oxygen tension of 40 mmHg with an oxyhemoglobin saturation of 75%. At normal Pa_{O_2}, approximately 56% ([90–40]/90) of dissolved oxygen is used. However, the volume of dissolved oxygen used is only 0.16 ml/dl, whereas the volume of oxygen used of that carried by hemoglobin is 4.7 ml/dl. Increasing arterial P_{O_2} by approximately 94 mmHg would add an amount of utilized oxygen from plasma (94 · 0.0031 = 0.29 ml/dl) that would be equivalent to the amount of oxygen utilized from that carried by 1 g of hemoglobin ([1.34 · (0.97– 0.75) = 0.29]). Thus, increasing Pa_{O_2} to more than 400 mmHg (augmenting Pa_{O_2} by 300 mmHg by increasing F_{IO_2}), as was accomplished in healthy volunteers in our studies,[12] should theoretically produce the same reduction in heart rate as 3 g of hemoglobin (fig. 4). This is consistent with our findings, where subjects breathing oxygen at a nadir hemoglobin of 5.6 g/dl had the same HR as was found during isovolemic hemodilution with these subjects breathing air at a hemoglobin concentration of approximately 8.9 g/dL (fig. 3). The effect of dissolved oxygen and its higher usability is true as well at higher concentrations of hemoglobin, although the relative size of the effect is reduced (fig. 5).
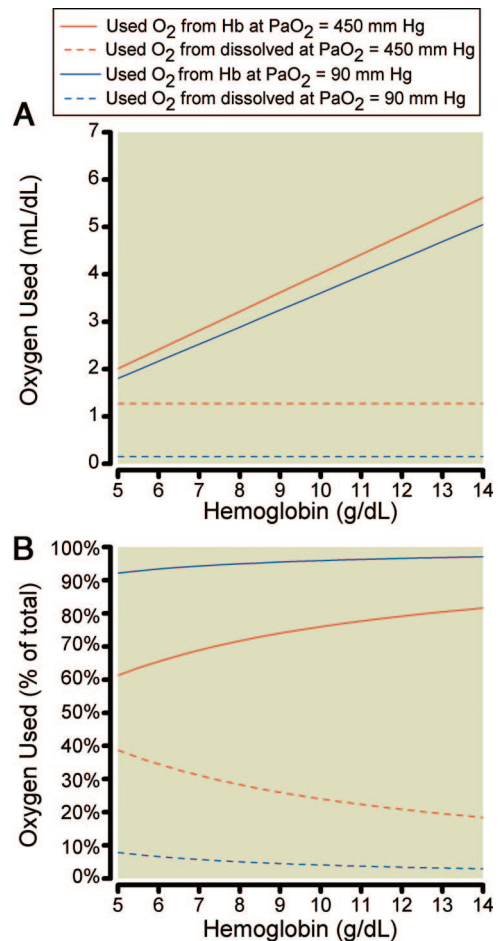

Fig. 5. Calculated data for the oxygen (O_2) used by tissues that came from hemoglobin and dissolved sources *versus* hemoglobin concentration. *A* shows the total oxygen used and *B* shows the percentage of oxygen used from 1) hemoglobin at Pa_{O_2} = 450 mm Hg (*solid red line*), 2) dissolved at Pa_{O_2} = 450 mm Hg (*dashed red line*), 3) hemoglobin at room air (RA), Pa_{O_2} = 90 mm Hg (*solid blue line*), 4) dissolved at RA, Pa_{O_2} = 90 mm Hg (*dashed blue line*).

Observing heart rate changes in response to higher F_{IO_2} in patients would be difficult. Many other factors affect HR clinically, including surgical stimulation, opioids, inhaled anesthetic agents, β-adrenergic antagonists, and patient comorbidities. HR also may not increase in response to anemia during general anesthesia.[18] Human volunteer studies such as ours are very robust, allowing repeated-measures analysis and control of confounding factors. Despite these issues in patients, the physiologic greater usability of dissolved oxygen would still be present. We would also emphasize that our model is of acute isovolemic anemia. Adequate cardiac output and tissue blood flow are necessary for the benefits of dissolved oxygen, which would not necessarily be present in the case of blood loss with significant hypovolemia.

This larger effect of increased utilization of dissolved oxygen at high F_{IO_2} has potentially important clinical and therapeutic implications. For example, treatment of patients with symptomatic anemia with supplemental oxygen could

be initiated while awaiting transfusion. In patients at risk for myocardial ischemia, short-term high F_{IO_2} has no risks, whereas rapid transfusion can precipitate circulatory overload and consequent pulmonary edema.[19,20] When erythrocyte transfusion is warranted in this group, it may be possible to proceed more slowly and safely with the administration of supplemental oxygen as a temporizing measure. High F_{IO_2} is often already used for patients under general anesthesia, in whom anemia may occur because of blood loss during surgery. Notably, the two editions of the American Society of Anesthesiologists Practice Guidelines for Blood Component Therapy did not been address this possibility.[21,22] In addition, supplemental oxygen has been shown to decrease HR after abdominal surgery.[23]

Treatment of anemia with oxygen has been shown to be effective in laboratory studies.[24–26] Ventilation with 100% oxygen decreases critical hemoglobin concentration[26] and reduces mortality,[25] myocardial ischemia, and signs of myocardial ischemia[24] in swine. Although these investigators recognized the greater relative contribution of dissolved oxygen toward the total amount of oxygen used at the lowest concentration of hemoglobin, these studies did not directly compare oxygen administration to transfusion.

Fontana *et al.* produced isovolemic hemodilution to a mean hemoglobin concentration of 3.0 g/dl, in children undergoing scoliosis surgery with an F_{IO_2} of 1, without evidence of inadequate tissue oxygenation.[27] Haque *et al.* found no decrease in HR but a decrease in cardiac output and stroke volume in patients with left ventricular failure given oxygen.[28] The effect of oxygen on cardiac output was considered an adverse effect, apparently based on the misconception that dissolved oxygen could not contribute a clinically significant amount despite the observed increases in mixed-venous P_{O_2}. Estimates of the efficacy of supplemental oxygen are still based on the effect on total oxygen content, not "usable" oxygen.

The substantial effect of increasing P_{aO_2} on the heart rate response to anemia raises the possibility that this could be an important factor in clinical trials concerned with anemia and transfusion, as much as a substantial increase in HR is associated with adverse cardiac outcomes in those with or at risk for cardiovascular disease,[7,8] and that risk is mitigated by lessening the HR increase by use of β-adrenergic antagonists.[29] Investigators should acknowledge this effect of breathing high oxygen concentrations in their study design and data analysis.

The receptor or transduction mechanism for increasing heart rate in response to anemia is not known. Our data describe the relationship, but do not address the mechanism. We found previously that this reflex/response could not be eliminated with β-adrenergic blockade using substantial doses of esmolol in conscious humans,[15] yet under general anesthesia, heart rate may not increase with anemia.[18] The importance of the carotid and aortic bodies in the physiologic responses, including heart rate, to anemia has produced inconsistent results in laboratory studies.[30–32] However, aortic chemoreceptor activation is not sufficient to explain the HR responses to anemia in humans, because humans lack active aortic chemoreceptors.[33]

Combining the data from several studies of similar volunteers allowed us to produce a substantial dataset, avoiding the necessity of performing repetitive studies that are physiologically challenging and invasive. We have extended our previous finding of a consistent linear increase in heart rate during anemia in unmedicated healthy volunteers, and that return of subjects' autologous erythrocytes reverses the HR response to anemia. Most importantly, we have shown that a high F_{IO_2} reverses the HR response to anemia. This is consistent with greater usability of dissolved oxygen. The benefit of high P_{aO_2} has potential clinical implications and its effect should also be considered in transfusion trial design and data analysis.

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