Published in final edited form as:

J Natl Med Assoc. 2010 November ; 102(11): 1000–1007.

The Relationship of Oxygen Transport and Cardiac Index for the Prevention of Sick Cell Crises

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Abstract

The formation of deoxyhemoglobin S (deoxy-Hb S) polymers is the key triggering event for the complex pathophysiologic manifestations of sickle cell anemia (SCA). This polymer formation is associated with a marked right-shifted oxyhemoglobin dissociation curve (decreased affinity, increased P_{50}), which results in a decrease in arterial oxygen saturation (SaO_2). There is a delay period (“delay time”) from the formation of deoxy-Hb S to polymerization that is markedly sensitive (to the power of 30–40) to the concentration and solubility changes of deoxy-Hb S. Deoxy-Hb S polymer formation leads to sickle cell vaso-occlusion, a unique characteristic of SCA. This theoretical study, which views SCA as a disease of oxygen transport, provides a novel framework to suggest that a small to modest increase in cardiac index (by decreasing the P_{50} and thus increasing the SaO_2) could change the distribution of the delay times (sec) such that the balance between occlusion and opening of microcirculatory vessels is shifted favoring the opening of these vessels, therefore disfavoring vaso-occlusion. Our approach integrates a mathematical model of oxygen transport in SCA with: (1) the expression relating the solubility of deoxy-Hb S to SaO_2 , and (2) the kinetic expression relating the delay time to the solubility of deoxy-Hb S.

Keywords

sickle cell anemia; heart

INTRODUCTION

Sickle cell anemia (SCA) is an inherited hemoglobinopathy characterized by the substitution of valine for glutamic acid at position of amino acid six in the β -globin chain of the hemoglobin molecule (sickle hemoglobin, Hb S). Under deoxygenating conditions, Hb S polymerizes inside the red blood cell, changing its shape into sickle cells. The hallmarks of SCA are a chronic hemolytic anemia and frequent painful vaso-occlusive episodes.

The problem of recurrent sickle cell crises can be considered one of tissue oxygen deprivation. As there are a number of major oxygen transport abnormalities in SCA, it is

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appropriate to consider a new approach to prevention from an oxygen transport perspective. This is the focus of this study. These oxygen transport abnormalities include: a chronic hemolytic anemia¹ (Hb range, 6–10 g/dL) and an increase in cardiac index (cardiac output, L/min/m²) at rest (Table 1),^{2–5} an additional increase in cardiac index with mild exercise (significant by the Wilcoxin Rank test),⁴ a decrease in arterial oxygen saturation (SaO₂) while breathing ambient air (Table 2),^{4,6,7} and normal to slightly increased oxygen consumption^{2,4,8} and resting energy expenditure.^{9,10} A major aberration is a marked right shift of the oxy-Hb S dissociation curve (decreased O₂ affinity, increased partial pressure of blood oxygen at 50% saturation [P₅₀]), which results in a decreased arterial oxygen saturation (SaO₂) while breathing ambient air (Figure 1). In patients with SCA, P₅₀ values in the Torr range^{11,12} of 30 to greater than 40 or even higher (50 to >60 Torr) have been reported.¹³ The oxygen transport abnormalities occur concomitantly with systemic oxidative stress^{14,15} and altered red blood cell rheology, which can lead to vaso-occlusive crises and end-organ damage, which limits cardiopulmonary reserve (additional volume of air that the lungs can inhale and exhale when breathing to the limit of capacity in times of stress).

The increase in cardiac index and the rightward shift of the oxyhemoglobin dissociation curve can be viewed as physiologic compensatory mechanisms that enable tissue oxygen demand to be met. As is true for compensatory mechanisms in many disease processes, it is the compensatory mechanisms themselves (ie, the systemic inflammatory response syndrome) that result in major pathophysiologic abnormalities. This is the case in SCA, where the rightward shift of the oxyhemoglobin dissociation curve results in a decrease in SaO₂ while breathing ambient air and the subsequent formation of deoxy-Hb S polymers. Oxy-Hb S does not form polymers. This polymer formation results in a decrease in red blood cell deformability and ultimately can lead to sickling. It is the key triggering event for the complex pathophysiologic manifestations of SCA and is directly related to the degree of arterial desaturation¹⁶ and Hb S concentration.

Under physiologic conditions, there is an apparent delay time from the formation of deoxy-Hb S to polymerization. This is a manifestation of the simultaneous occurrence of 2 nucleation pathways: (1) homogenous nucleation, where nuclei form in solution; and (2) heterogeneous nucleation, where nuclei form on existing polymers.¹⁷ This description of the underlying mechanism of deoxy-Hb S polymerization applies equally to solutions and intracellular deoxy-Hb S.¹⁸ The delay time is a function of both the concentration and solubility of deoxy-Hb S. This relationship can be expressed by the following equation:¹⁸

$$1/D_T = r(S)^{30} \quad [1]$$

D_T is the delay time, r is an experimental constant ($1 \times 10^{-6} \text{sec}^{-1}$) and S is the supersaturation ratio. S is the concentration of deoxy-Hb S (g/cc)/solubility of deoxy-Hb S (g/cc).

This marked dependence of the D_T on the supersaturation ratio is the “highest known concentration dependence for a process taking place in solution.”¹⁹ The kinetics of deoxy-Hb S polymerization are such that small changes in the solubility of deoxy-Hb S can markedly affect the D_T . This is demonstrated in Figure 2, where the fractional change in solubility of deoxy-Hb S is related to the log₁₀ value of the D_T for varying values of D_T (1–40 sec) prior to changes in deoxy-Hb S solubility.

The solubility of deoxy-Hb S is directly related to the fractional saturation of oxygen in the blood (Equation 9 and Tables 3–6), which is a function of the P₅₀ when breathing ambient

air. As an increase in P_{50} can be viewed as a physiologic defense mechanism to increase tissue oxygen delivery to the tissues, it is potentially responsive to cardiac index.

Based on the discussion above, it should be theoretically possible to manipulate oxygen transport by increasing the cardiac index. To the degree in which P_{50} is responsive, this should result in increased delay times and should have a beneficial effect in the SCA patient, decreasing vaso-occlusion and the severity of sickle cell vaso-occlusive crises. To further explore this concept, a mathematical model of global oxygen transport in SCA is presented.

METHODS

The model, which presumes that P_{50} is responsive to cardiac index, was developed to solve for cardiac index ($L/min/m^2$) with varying levels of hemoglobin concentration (Hb) (6–10 g/dL at intervals of 1 g/dL), oxygen consumption (VO_2) (100–250 mL/min/ m^2 at intervals of 50 mL/min/ m^2), and P_{50} (28–50 Torr at intervals of 2 Torr) while breathing ambient air (assumed partial pressure of arterial oxygen [PaO_2] is 81 Torr). The partial pressure of mixed venous oxygen (PvO_2) was fixed at 40 Torr. This was based on the well-known model of the microcirculation in SCA where the capillary PO_2 was fixed at 40 Torr.²⁰ The model was constructed using the Fick global oxygen transport equation:

$$Q = \frac{VO_2}{(Ca - Cv)(10)} \quad [2]$$

where Q is cardiac index ($L/min/m^2$), Ca is arterial oxygen content (volumes %), and Cv is mixed venous oxygen content (volumes %).

Equation 2 was expanded to include the components of Ca and Cv :

$$Q = \frac{VO_2}{\{[(Hb)(SaO_2)(1.36) + PaO_2(0.0031)] - [(Hb)(SvO_2)(1.36) + PvO_2(0.0031)]\}} \quad [3]$$

Mixed venous oxygen saturation (SvO_2) is obtained by using the SvO_2 solution for the Hill equation.

$$SvO_2 = \frac{1}{(P_{50}/PvO_2)^{2.65} + 1} \quad [4]$$

For this model, the following equation was used:

$$SvO_2 = \frac{1}{[P_{50}/40]^{2.65} + 1} \quad [5]$$

SaO_2 was determined by using the Hill equation solution for SvO_2 applied to arterial blood.

$$SaO_2 = \frac{1}{[(P_{50}/PaO_2)^{2.65} + 1]} \quad [6]$$

For this model, the following equation was used:

$$\text{SaO}_2 = \frac{1}{(\text{P}_{50}/81)^{2.65} + 1} \quad [7]$$

The error involved in using the Hill equation for determining SaO_2 should be minimal, as the fractional inspiratory concentration of oxygen is not increased on ambient air and the SaO_2 decreases with increasing levels of P_{50} . In addition, the values of SaO_2 obtained by this method (Tables 3–6) are similar to those values reported in the literature for SCA (Table 2).

The following equation expresses the solubility of deoxy-Hb S (Cs) as a function of temperature ($^{\circ}\text{C}$):²¹

$$\text{Cs (g/cc)} = 0.321 - 0.00883\text{T} + 0.00125\text{T}^2 + 0.0924\text{Y} + 0.0980\text{Y}^2 + 0.235\text{Y}^{15} \quad [8]$$

where $\text{Y} = \text{SaO}_2$.

For $\text{T} = 37^{\circ}\text{C}$, Equation 8 becomes:

$$\text{Cs (g/cc)} = 0.165 + 0.0924\text{Y} + 0.0980\text{Y}^2 + 0.235\text{Y}^{15} \text{ (reference}^{21}) \quad [9]$$

Equation 9 was used to calculate the solubility of deoxy-Hb S in the model.

RESULTS

The results from the model are shown in Tables 3 to 6. At each level of hemoglobin and oxygen consumption, an increased cardiac index results in a decreased P_{50} and thus an increased SaO_2 and deoxy-Hb S solubility. For a given increase in cardiac index, a higher Hb, a higher P_{50} , and lower oxygen consumption results in a greater increase in deoxy-Hb S solubility. Figure 2, which is based on Equation 1, demonstrates the logarithmic increase in D_T by different populations of cells (based on D_T) as the solubility of deoxy-Hb S is increased (homozygous sickle cell disease is assumed).

DISCUSSION

In approaching the problem of symptomatic SCA by attempting to increase the oxyhemoglobin affinity, the role of the D_T in relation to the circulatory transit times must be considered. The circulatory transit times are 1 to 2 seconds for the arterial circulation, 1 second for the microcirculation, and 15 seconds for the venous circulation to the lungs.²¹ Approximately 10% of red blood cells in the arterial circulation and 20% of red blood cells in the venous circulation are sickled.¹⁹ The sickled cells present in the venous circulation have a D_T less than 15 seconds. Most of these cells will be depolymerized in the lungs and do not lead to circulatory red blood cell occlusion. Although occlusion may not occur, the red blood cell membrane can be damaged by the sickling process. This membrane damage can result in intracellular hemo-concentration and subsequent shortening of the D_T .²¹

Relative to the large number of circulating sickled cells (10^{12}) that are “normally” present in the circulation, the low incidence of vaso-occlusive crises can be explained by a balance of the rates of occlusion and opening of occluded microcirculatory vessels.¹⁹ While the

specific etiology of sickle cell crises is not completely understood, several variables have been associated with their onset. These include fever, hypoxia, increased temperature, acidosis, dehydration, alterations in vascular tone, and psychological stress.²² It is apparent that the D_T distribution is a critical factor in determining whether a vaso-occlusive crisis will occur.

There are 2 plausible circumstances in which relatively small changes in the D_T would have the potential to markedly improve SCA pathophysiology. In the first case, red blood cells with a relatively short D_T (ie, ≤ 2 sec) have the potential to sickle in the microcirculation as these cells become desaturated when they release oxygen to the tissues. Many of these red blood cells did not completely depolymerize in the lungs and thus will have a short D_T because of the rapidity of heterogeneous nucleation in the presence of existing intracellular polymer.²¹ Thus, a small increase in D_T would shift the balance of occlusion to the opening of vessels in the microcirculation. The second case is related to red blood cells that polymerize on the venous side of the circulation with a D_T close to the transit time from the microcirculation to the lung (approximately 15 sec). A small increase in the D_T (3–4 sec) would keep red blood cells from undergoing repeated cycles of polymerization and subsequent membrane damage.

Sickling occurs because of a high intracellular Hb S concentration (mean corpuscular hemoglobin concentration, 40–50 g/dL) relative to its solubility, which is a function of SaO_2 (Equation 9). Although there is a wide distribution of intracellular Hb S, it has been demonstrated that sickling does not occur in the absence of the high-density red blood cell fraction (dehydrated red blood cells with a high concentration of Hb S).²³ Nevertheless, the distribution of D_T is a critical factor in determining the occurrence of a vaso-occlusive crisis. The importance of the D_T and its marked sensitivity to the effect of SaO_2 on the solubility and concentration of Hb S underlie the approach put forward in this paper. While increasing oxygen affinity for hemoglobin remains a potentially attractive therapeutic approach, no effective therapeutic modalities have been developed. Conceptually, agents or therapeutic modalities directly increasing oxygen affinity for hemoglobin could interfere with a normal physiologic mechanism that increases tissue oxygen delivery.

Increasing cardiac index (and SaO_2) as an approach to ameliorating the symptoms and subsequent end-organ damage in SCA is theoretically attractive on 2 fronts. First, increasing oxygen delivery to the tissues could potentially decrease the stimulus for increased red blood cell 2,3-diphosphoglycerate (2,3-DPG) production, thus increasing the affinity of oxygen for hemoglobin, leading to increased SaO_2 . The solubility of Hb S can be markedly affected by 2,3-DPG. It has been shown²⁴ that under physiologic conditions a saturated solution of 2,3-DPG can decrease the solubility of deoxy-Hb S by up to 9%. Second, an increase in cardiac index could result in augmentation of microvascular flow, which would have a positive rheologic effect.

To validate our concept from a theoretical point of view, we have extrapolated changes in deoxy-Hb solubility (some of which are taken from the tables presented) on the semilogarithmic grid depicted in Figure 2 that relates changes in deoxy-Hb S solubility to delay times. A 0.09 fractional change (9% change) in deoxy-Hb S solubility will produce dramatic changes in the delay times. If the D_T prior to the change in solubility was 1 second, a 9% increase in solubility would result in the D_T being increased to a $\log_{10}$ value of approximately 1.1 (12.5 sec). If the D_T prior to the change in solubility was 15 seconds, it would be increased to a $\log_{10}$ value of approximately 2.25 (178 sec). Even a small percent change could be remarkably beneficial. If the delay time prior to the change in solubility was 15 seconds, a 2% increase in solubility would increase the D_T 26 seconds (a $\log_{10}$ value

of approximately 1.42) This would keep those deoxy-Hb S red blood cells from polymerizing in the venous side of the circulation.

Similarly, results from Tables 3 to 6 could be extrapolated in Figure 2 to estimate potential D_T changes for red blood cell populations with different underlying delay times (1–40 sec) related to changes in cardiac index with varying levels of Hb, VO_2 , and P_{50} . The following clinical scenarios demonstrate the potential benefit of manipulating oxygen transport to affect red blood cell delay times:

1. From Table 4: For a patient with a VO_2 of 150 mL/min/m², a Hb of 8 g/dl, and a P_{50} of 46 Torr, an increase in cardiac output by 0.35 L/min/m² represents a potential increase in deoxy-Hb solubility from 0.306 to 0.337 g/cc (a 10.1% increase). If only one-fifth of the increase in cardiac output was effective in terms of oxyhemoglobin affinity (a 2% increase in solubility), this would translate to an increase in the D_T from 15 to 27 seconds (a 1.47 log₁₀ value). These red blood cells would clearly avoid sickling on the venous side of the circulation. If all of the increase in cardiac output was effective in terms of oxyhemoglobin affinity, it would have a dramatic effect on the delay times. For those red blood cells with a D_T of 15 seconds, the D_T would then increase to greater than 260 seconds (an approximate 2.4 log₁₀ value). For those red blood cells with a 2-second D_T (not shown in Figure 2), a 2% increase in solubility would translate to a 3.6-second D_T (an approximate 0.56 log₁₀ value). It is unlikely that these red blood cells would sickle in the microcirculation.
2. From Table 5: For a patient with a VO_2 of 200 mL/min/m², a Hb of 9 g/dl, and a P_{50} of 44 Torr, an increase in cardiac output by 0.6 L/min/m² represents a potential 10.8% increase in deoxy-Hb S solubility (from 0.314–0.348 g/cc). If all of the increase in cardiac output was effective in terms of oxyhemoglobin affinity, all deoxy-Hb S red blood cells with a 1-second D_T would have increased their D_T to a 1.25 log₁₀ value (17.8 sec) and likely would not sickle in the microcirculation. Those red blood cells with a D_T of 15 seconds would now have a D_T of approximately a 2.4 log₁₀ value (251 sec). If only one-third of the increase in cardiac output was effective in terms of oxyhemoglobin affinity (a 3.6% increase in solubility), those red blood cells with a 1-second D_T would now have a D_T of approximately a 0.46 log₁₀ value (2.9 sec). Those red blood cells with a 15-second D_T would now have a D_T of approximately a 1.64 log₁₀ value (43.6 sec).

These calculations demonstrate that if our concept is valid, only a small to modest increase in cardiac index is needed to dramatically affect the vaso-occlusive course of SCA in selected patients in terms of P_{50} , VO_2 , and Hb. Thus, it could be considered beneficial to increase cardiac index in chronically anemic SCA patients whose cardiac index is typically elevated. There is some evidence that could support this approach. First, it has been reported that patients with SCA, including children, showed a decreased left ventricular contractile performance despite having elevated cardiac indices and normal ejection fractions. The evidence was based on significant decreases in the ratio of end-systolic stress to end-systolic volume index and the slope of the end-systolic vs end-systolic volume index relation.⁵ Second, evidence of left ventricular dysfunction was identified in a larger study of 124 children.²⁵ The results of these studies suggest that the increase in cardiac index in SCA is associated with an increase in preload and afterload and is not related to an increase in cardiac contractility. Thus, regardless of any oxyhemoglobin affinity effect, it may be beneficial for patients with SCA to increase cardiac contractility even in the absence of overt heart failure. Nevertheless, further studies exploring the association between cardiac index and vaso-occlusion are warranted.

Our concept may be explained, at least in part, by findings of an intriguing case report documenting dramatic relief from episodes of sickle cell pain with angiotensin I-converting enzyme (ACE) inhibitor (Trandolapril).²⁶ The authors postulate that angiotensin I-converting enzyme was activated by tissue hypoxia. ACE inhibitors have been shown to decrease arterial wall stiffness²⁷ and in some circumstances to increase microvascular density,²⁸ both of which have the potential to improve tissue oxygen delivery. In addition, in the presence of heart failure, ACE inhibitors could improve cardiac index by after-load reduction. This mechanism is in line with the concept and approach outlined in this paper. The concept presented in this paper could be also evaluated in the transgenic mice SCA model²⁹ in studies in which the effect of agents to increase myocardial contractility could be assessed.³⁰

In summary, the theoretical calculations presented in this paper suggest that in certain clinical situations defined by the oxygen transport parameters, small increases in cardiac index could have the potential to affect dramatically the incidence of the vaso-occlusive crises in SCA. If indeed, the oxyhemoglobin affinity responds to small increases in cardiac output, it could lead to a decrease in the incidence of vaso-occlusive crises. A clinically significant result could be less end-organ damage and perhaps a lessening of the severity of the associated chronic hemolytic anemia.

Acknowledgments

Funding/Support: Partial funding for this activity came from the Department of Health and Human Services/Office of Minority Health (MPCMP081013 B OMH-MMC-1-09).

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Figure 1.
Decrease in Oxygen Saturation With Right-Shifted Oxyhemoglobin Dissociation Curve
While Breathing Ambient Air

Figure 2.
Effect of Hemoglobin S Solubility on Time Delay

Table 1

Cardiac Index in Sickle Cell Anemia

No. of Subjects	Mean Age ($\pm$ SD), y	Age Range, y	CI (L/min/m ²) ($\pm$ SD)	CI (L/min/m ²) Range	Reference No.
39	22 ($\pm$ 5)	15–37	5.6 ($\pm$ 0.2)	ND	2
6	26.2 ($\pm$ 10.2)	14–36	4.8 ($\pm$ 0.6)	3.4–5.4	3
10	22 ($\pm$ 6.8)	13–37	6.1 ($\pm$ 0.8)	5.3–8.3	4
6	31 ($\pm$ 7)	ND	5.0 ($\pm$ 1.4)	ND	5
6 ^a	12 ($\pm$ 4)	ND	4.6 ($\pm$ 0.8)	ND	5

Abbreviations: CI, cardiac index; ND, not determined.

^aData was taken from the literature as indicated by their reference number. All subjects were diagnosed clinically as having sickle cell anemia except for those corresponding to reference 4. Some of the diagnoses were confirmed by hemoglobin electrophoresis.

Table 2

Arterial Oxygen Saturation at Ambient Air in Patients With Sickle Cell Anemia

No. of Subjects	Mean Age ($\pm$ SD), y	Age Range, y	Mean SaO ₂ (%) ($\pm$ SD)	Range SaO ₂ (%)	Reference No.
10	22.0 ($\pm$ 6.8)	13–37	91.6 ($\pm$ 3.2)	86.9–97.5	4 ^a
9	25.0 ($\pm$ 9.3)	12–40	88.3 ($\pm$ 4.3)	80.0–92.6	6 ^b
10	25.7 ($\pm$ 12.3)	16–49	86.6 ($\pm$ 5.3)	79.5–97.0	7 ^c

^aConfirmatory hemoglobin electrophoresis done in some of the patients.^bNo information on hemoglobin genotypes for patients.^cNo patients had hemoglobins other than S, F, and A2.

Table 3

Theoretical Distribution of Increasing Cardiac Index, Deoxyhemoglobin S Solubility at a Fixed Oxygen Consumption of 100 mL/min/m² for Different Hemoglobin Concentrations

Hb, g/dL													
6	Cl, L/min/m ²	2.80	2.80	2.90	3.00	3.10	3.20	3.40	3.60	3.80	4.20	4.60	5.10
7	Cl, L/min/m ²	2.40	2.40	2.50	2.60	2.65	2.80	2.90	3.20	3.30	3.60	4.00	4.40
8	Cl, L/min/m ²	2.10	2.10	2.20	2.20	2.30	2.40	2.60	2.70	2.90	3.20	3.50	3.90
9	Cl, L/min/m ²	1.90	1.90	1.95	2.00	2.10	2.20	2.30	2.40	2.60	2.80	3.10	3.50
10	Cl, L/min/m ²	1.70	1.70	1.80	1.80	1.90	2.00	2.10	2.20	2.35	2.60	2.80	3.20
P ₅₀ , Torr		50	48	46	44	42	40	38	36	34	32	30	28
SaO ₂ , %		0.780	0.800	0.817	0.834	0.851	0.866	0.881	0.896	0.909	0.921	0.933	0.943

Abbreviations: CI, cardiac index; Hb, hemoglobin.

Table 4

Theoretical Distribution of Increasing Cardiac Index and Deoxyhemoglobin S Solubility at a Fixed Oxygen Consumption of 150 mL/min·m² for Different Hemoglobin Concentrations

Hb, g/dL													
6	CI, L/min/m ²	4.20	4.20	4.30	4.45	4.60	4.80	5.10	5.40	5.80	6.30	6.90	7.70
7	CI, L/min/m ²	3.60	3.60	3.70	3.80	4.00	4.15	4.40	4.60	5.00	5.40	6.00	6.70
8	CI, L/min/m ²	3.20	3.20	3.30	3.40	3.50	3.65	3.80	4.10	4.40	4.80	5.20	5.90
9	CI, L/min/m ²	2.80	2.85	2.90	3.00	3.10	3.25	3.40	3.60	3.90	4.30	4.70	5.25
10	CI, L/min/m ²	2.50	2.60	2.60	2.70	2.80	2.90	3.10	3.40	3.50	3.85	4.20	4.70
	P ₅₀ , Torr	50	48	46	44	42	40	38	36	34	32	30	28
	SaO ₂ , %	0.780	0.800	0.817	0.834	0.851	0.866	0.881	0.896	0.909	0.921	0.933	0.943
	Deoxy-Hb S solubility, g/cc	0.290	0.297	0.306	0.314	0.325	0.337	0.348	0.363	0.379	0.395	0.414	0.432

Abbreviations: CI, cardiac index; Hb, hemoglobin.

Theoretical Distribution of Increasing Cardiac Index and Deoxyhemoglobin S Solubility at a Fixed Oxygen Consumption of 200 mL/min/m² for Different Hemoglobin Concentrations

Abbreviations: CI, cardiac index; Hb, hemoglobin.

Table 6

Theoretical Distribution of Increasing Cardiac Index and Deoxyhemoglobin S Solubility at a Fixed Oxygen Consumption of 250 mL/min/m² for Different Hemoglobin Concentrations

Hb, g/dL		7.00	7.05	7.20	7.40	7.70	8.00	8.30	8.90	9.60	10.50	11.50	12.80
6	CI, L/min/m ²	6.00	6.10	6.20	6.40	6.60	6.90	7.30	7.70	8.30	9.00	9.90	11.10
7	CI, L/min/m ²	5.30	5.30	5.50	5.60	5.80	6.10	6.40	6.80	7.30	7.95	8.70	9.80
8	CI, L/min/m ²	4.70	4.75	4.90	5.00	5.20	5.40	5.70	6.05	6.50	7.10	7.80	8.75
9	CI, L/min/m ²	4.20	4.30	4.40	4.50	4.70	4.90	5.15	4.60	5.90	6.40	7.10	7.90
10	CI, L/min/m ²	50	48	46	44	42	40	38	36	34	32	30	28
P ₅₀ , Torr		0.780	0.800	0.817	0.834	0.851	0.866	0.881	0.896	0.909	0.921	0.933	0.943
SaO ₂ , %		0.290	0.297	0.306	0.314	0.325	0.337	0.348	0.363	0.379	0.395	0.414	0.432
Deoxy-Hb S Solubility, g/cc													

Abbreviations: CI, cardiac index; Hb, hemoglobin.