Review of physiologic mechanisms in response to anemia

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Abstract

Objective: To determine the nature and quality of the physiologic evidence regarding an "optimum" hemoglobin concentration in anemic patients or in patients with specific diseases.

Literature search and selection: Searches of MEDLINE from January 1966 to December 1996 were combined with manual searches of the bibliographies and references from experts. Citations were chosen by 2 reviewers if they were related to red blood cell transfusion practice and, more specifically, to physiologic adaptation to anemia. Disagreement was resolved through consensus.

Literature synthesis: The articles selected from the literature search were classified by study design and topic areas. Evidence-based inferences were derived from the literature.

Results: Of the 160 articles included in this review, 58 (36%) were human studies and 102 (64%) were laboratory studies. Most studies (84) fell into the "hemodilution" category, and were predominantly in animal models (70). Overall, 90 studies (56%) used a valid design with appropriate experimental and concurrent control groups (graded as level I or II). The distribution of grading was uniform throughout the categories. The quality of the evidence was deemed weaker for laboratory studies evaluating cardiac adaptation to anemia, largely because of a lack of reported concurrent controls in most studies. Inferences drawn from the literature were graded on a 4-point scale assessing the quality of the evidence; 13 of 18 statements were given the highest grade. The clinical significance of the Bohr effect and the shifts in the oxyhemoglobin curve following changes in pH were thought to be poorly studied and were rated lowest. The studies evaluating maximum oxygen delivery in anemia were rated as weak, partly because of conflicting reports. Of all identified studies, 56% were well designed and reported. Important adaptive responses to anemia consist of an elevation of cardiac output and its redistribution to favour the coronary and cerebral circulations at the expense of the splanchnic vascular beds; studies supporting these statements were rated highly. The evidence also suggests that patients with cardiac disease are at risk of adverse events from anemia.

Conclusions: There is a significant body of evidence supporting cardiovascular adaptive responses to anemia. However, there is a remarkable lack, in both quality and quantity, of clinical studies addressing how the "normal" physiologic adaptations may be affected by a variety of diseases. The physiologic evidence alone is insufficient to inform most decisions about red blood cell transfusion.

Many of the physiologic concepts in oxygen (O_2) transport and utilization were described in the early part of the century and are still widely accepted.[1] In 1920, Barcroft[2] noted that tissue oxygenation was a function of hemoglobin concentration ([Hb]), oxygenation of blood by the lungs and cardiac output. Similarly, many of the principles underlying the transfer of O_2 from the microcirculation to the mitochondria are well established and have stood the test of time.[1]

Although much of the basic physiology underlying the delivery of O_2 has been extensively studied,[1,3–5] there are few, if any, systematic, comprehensive evaluations of the quality of the evidence in laboratory and clinical studies in

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anemia. By adapting recently proposed principles for systematic reviews,[6–8] we provide a detailed and critical appraisal of the physiologic literature, addressing primarily the following questions: Does the evidence from physiologic studies suggest an "optimal" [Hb] for the majority of anemic patients or patients with specific diseases? Are certain patients at increased risk from the physiologic consequences of anemia? Thus, this systematic review will provide the practising physician with a simplified synthesis of physiologic information relevant to decisions about red blood cell (RBC) transfusion. To fulfill this objective, some of the more complex mechanisms were deliberately omitted or oversimplified.

Literature search and selection

A search of MEDLINE from January 1966 to July 1996 was constructed using the following medical subject headings (MeSHs): blood transfusion, erythrocyte transfusion, blood component transfusion. The strategy involved searching the database for the presence of these terms as keywords and text words in the titles and abstracts of all citations. The results were combined with a specific MEDLINE search during the same time period that used the MeSHs: blood transfusion, oxygen, cerebral artery, cerebral artery disease, cerebral ischemia, cerebrovascular circulation, subarachnoid hemorrhage, coronary circulation, coronary disease, coronary vessels. No limitations were placed on the computer searches; therefore, all types of studies in all languages were initially included. Bibliographies were searched manually and additional studies were identified by contacting Canadian experts in O_2 kinetics, physiology and microcirculation. Citations and abstracts generated through the MEDLINE searches were scanned by 2 reviewers.

Articles were initially selected because of their relevance to RBC and plasma transfusion practice. A second step focused on selecting articles that addressed the physiologic responses to anemia and red cell transfusions. The final selection of articles was also limited to studies with an English or French abstract. Articles were categorized according to topic and study type. Data from all articles were gathered, interpreted and summarized by two authors. From the synthesis of the information, the quality of evidence for each of the summary statements was also tabulated and agreed upon. The clinical evidence was graded according to the classification of Wolfe.[9] Given that physiologic concepts were considered in this systematic overview, we also graded laboratory studies and the evidence derived from such studies (Table 1). All disagreements in the selection and interpretation of studies were resolved through consensus.

Results

Computer searches yielded 8426 citations. Of these, 1424 articles were determined to be relevant to CPGs on the use of RBCs and plasma. Among them, 160 articles addressed aspects of physiologic mechanisms in anemia (Table 2): 58 (36%) were human studies and 102 (64%) were laboratory studies. The greatest number of studies (84) were in the category "hemodilution," predominantly conducted in animal models (70). Normovolemic hemodilution was the most common model in the study of adaptive physiologic mechanisms in anemia.

Table 1. System used to grade studies

Level of evidence	Description of criteria*
Individual studies	
LI	Concurrent controls used (random allocation should be used wherever possible). Experimental methods proven valid (at a minimum, appropriate positive and negative controls must be described). Objective primary measure(s) or objective interpretation of measure(s). Demonstrates relevant difference between groups (not limited to statistical significance). Study conducted in humans or in an experimental model representative of human biological process(es).
LII	Concurrent controls used. All previous criteria present but major limitation(s) in the application of model to humans; small sample size or difference(s) among groups are not significant.
LIII	Control group not concurrent Major limitation in the primary outcome measure(s) or Experimental methods not reproducible or valid.
LIV	Controls not used.
Inferences from all studies	
Ci	Inferences based on at least two LI studies from independent investigators. No LI studies demonstrating conflicting results.
Cii	Inferences based on one LI study with no conflicting LI or LII evidence.
Ciii	Inferences based on at least one LII study with no conflicting LII evidence.
Civ	Inferences based on theory, LIII or LIV studies or conflicting LI or LII evidence.

* Criteria are designed to grade studies evaluating biologic processes, not to evaluate outcomes from therapy. Studies evaluating outcome measures similar to clinical outcomes in the laboratory setting (e.g., a survival study in an animal model) should use rigorous experimental designs comparable to human studies (i.e., a double-blind randomized controlled clinical trial is optimal).

Overall, 90 studies (56%) used a valid design with appropriate experimental and concurrent control groups (graded as LI or LII). The distribution of grading was uniform throughout the categories. The quality of the evidence was deemed weaker for laboratory studies evaluating cardiac adaptation to anemia, largely because of a lack of reported concurrent controls in most studies.

The 18 statements reflecting inferences drawn from the literature were graded according to a 4-point scale (Table 3); 13 were given the highest rating (Ci) based on assessment of the quality of the evidence. The clinical significance of the Bohr effect and shifts in the oxyhemoglobin curve were thought to be poorly studied and were rated accordingly (Civ). The studies evaluating maximum O_2 delivery in anemia were rated as weak, partly because of conflicting reports.

Overview of O_2 transport

Detailed reviews of the physiologic principles of O_2 transport may be found in textbooks and review articles.[1,4,5] Hemoglobin is a complex molecule consisting of 4 globin moieties, each incorporating an iron-containing heme ring where O_2 is bound according to its partial pressure (PO_2). The O_2 binding affinity of hemoglobin is illustrated by the sinusoidal relationship between hemoglobin O_2 saturation and PO_2 (Fig. 1). This relationship, referred to as the oxyhemoglobin dissociation curve, enables both efficient loading in the lungs at high PO_2 and efficient unloading in the tissues at low PO_2 levels. However, the O_2 binding affinity of hemoglobin (the degree to which O_2 molecules saturate the hemoglobin binding sites at a given PO_2) may be altered by various disease states and may play a significant adaptive role in response to anemia.

The amount of O_2 delivered, either to the whole body or to specific organs, is the product of blood flow and arterial O_2 content. For the whole body, O_2 delivery (DO_2) is the product of total blood flow or cardiac output (CO) and arterial O_2 content (CaO_2):

$$DO_2 = CO \times CaO_2 \quad [1]$$

When a person is breathing ambient air under nor-

Table 2: Grading of studies evaluating biological processes

		Level of evidence			
Topic of study	No, (%)	LI	LII	LIII	LI
O_2 delivery and consumption	27 (16.8)				
Human	24 (15.0)	12	2	9	1
Laboratory	3 (1.9)	2	0	1	0
Adaptation to anemia or transfusions	49 (30.6)				
Cardiac adaptation					
Human	8 (5.0)	0	0	6	2
Laboratory	23 (14.4)	0	17	6	0
Microcirculation and viscosity					
Human	1 (0.6)	0	1	0	0
Laboratory	5 (3.1)	3	2	0	0
Oxyhemoglobin dissociation curve and 2,3-DPG concentration studies	12 (7.5)	3	5	2	2
Hemodilution	84 (52.5)				
Cardiovascular effect*					
Human	4 (2.5)	0	2	2	
Laboratory	17 (10.6)	10	1	6	0
Coronary flow studies					0
Human	7 (4.4)	3	1	2	
Laboratory	47 (29.4)	16	2	28	1
Cerebral flow studies					1
Human	3 (1.9)	1	1	1	
Laboratory	4 (2.5)	4	0	0	0
Other organ flow	2 (1.3)	0.00	2	0.00	0
Total human studies	58 (36.3)	19	11	22	6
Total laboratory studies	102 (63.8)	35	25	41	1
Total		54	36	63	7
%	160	33.8	22.5	39.4	4.4

Note: 2,3-DPG = 2,3-diphosphoglycerate.
*We differentiated between studies focusing on mechanisms of cardiac adaptation and those looking at the cardiovascular effects of hemodilution.

mal conditions, the O_2 present in their arterial blood is bound to hemoglobin. When fully saturated, 1 g of hemoglobin binds 1.39 mL of O_2. A small amount is also dissolved in plasma water. The negligible amount of dissolved O_2 is directly proportional to the partial pressure and may be calculated by multiplying PO_2 by a constant (k = 0.00301 mL/mL per mm Hg), termed the solubility coefficient. Thus, under most circumstances, arterial O_2 content may be estimated from the portion bound to hemoglobin using the equation:

$$CaO_2 \text{ (in mL/L)} = \% \text{ saturation} \times 1.39 \text{ (mL/g)} \times [\text{Hb}] \text{ (g/L)} \quad [2]$$

If we substitute CaO_2 from [2] into [1], then:

$$DO_2 = CO \times (\% \text{ saturation} \times 1.39 \times [\text{Hb}]) \quad [3]$$

Where, CO is cardiac output in L/min and % saturation is the percentage of hemoglobin saturated with O_2.

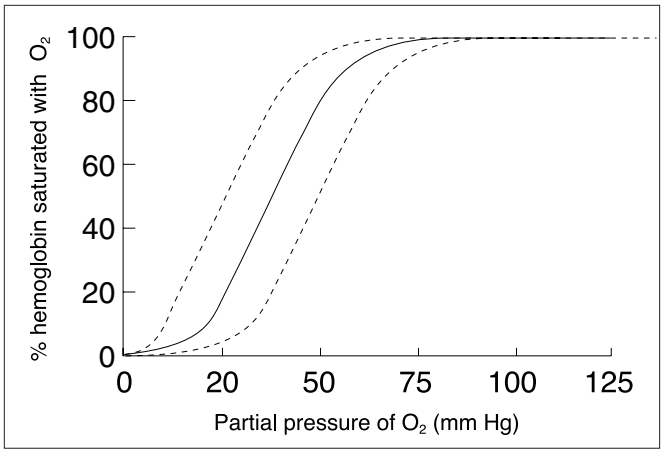

Fig. 1: The oxyhemoglobin dissociation curve. The solid line represents O_2 binding affinity to the hemoglobin molecule at standard temperature (37°C) and pH (7.4). The dashed lines represent hypothetical shifts in the curve: to the right with increased 2,3-diphosphoglycerate (2,3-DPG) levels or decreased temperature or pH; to the left with decreased 2,3-DPG or increased temperature or pH.

CO, a measure of blood flow to the entire body, is the other major determinant of O_2 delivery. It may be quantified by multiplying the stroke volume (the difference between end diastolic volume and end systolic volume in millilitres) and heart rate (in beats per minute). Stroke volume is influenced by preload (end diastolic volume affected by filling pressure), afterload (the arterial pressure and resistance encountered during each ventricular ejection) and contractility (the force generated during a contraction). The majority of O_2 consumed by the heart is expended by the contracting myocyte. The heart requires a continuous supply of O_2 via the coronary circulation. This supply is tightly coupled to metabolic demand, primarily through regulated blood flow rather than increased O_2 extraction. The O_2 supply–demand relation is mediated by metabolic byproducts such as adenosine.[183]

Table 3: Inferences drawn from and the quality of evidence graded by 2 observers

Inference	Quality of evidence
Oxyhemoglobin dissociation curve	
Anemia shifts the oxyhemoglobin curve to the right because of increased 2,3-DPG levels	Ci
Anemia causes clinically significant rightward shifts in the oxyhemoglobin curve because of the Bohr effect	Civ
The shift in the oxyhemoglobin curve has been clearly established in many forms of anemia (excluding hemoglobinopathies)	Cii
The shift in the oxyhemoglobin curve has been clearly established in a number of human diseases	Civ
Cardiac output	
Cardiac output increases with increasing degrees of normovolemic anemia provided that blood volume is adequate	Ci
Increased cardiac output in normovolemic anemia is a result of increased stroke volume	Ci
The contribution of increased heart rate to the increase in cardiac output following normovolemic anemia is variable	Ci
Other hemodynamic alteration	
Changes in blood viscosity result in many of the hemodynamic changes in normovolemic anemia	Ci
Normovolemic anemia is accompanied by increased sympathetic activity	Ci
Normovolemic anemia causes increased myocardial contractility	Cii
Normovolemic anemia causes a decrease in systemic vascular resistance	Ci
Normovolemic anemia results in a redistribution of cardiac output toward the heart and brain and away from the splanchnic circulation	Ci
Maximum global O_2 delivery occurs at hemoglobin concentrations ([Hb]) of 100–110 g/L	Ciii
Global O_2 delivery declines above and below [Hb] of 100–160 g/L	Ci
Coronary and cerebral blood flow	
Coronary blood flow is increased during anemia	Ci
Cerebral blood flow is increased during anemia	Ci
Coronary artery disease in the presence of moderate degrees of anemia ([Hb] below 90 g/L) results in impaired left ventricle contractility or ischemia	Ci
Moderate anemia does not aggravate cerebral ischemia in patients with cerebrovascular disease	Ci

Note: 2,3-DPG = 2,3-diphosphoglycerate.

During a ventricular contraction, there is an increase in pressure followed by ejection of a fraction of the ventricular volume. Whereas, changes in both pressure and volume are needed to perform work (work in the physical sense is the product of pressure and volume), the rate of O_2 consumption or energy expenditure by the heart is less for a change in volume than for a comparable change in pressure.[184,185]

However, according to Laplace's Law:

$$T = (P \times R)/H \quad [4]$$

where T is wall tension, P is intracavitary pressure, R is radius and H is wall thickness. Greater wall tension is generated in ejecting a given stroke volume if the radius is increased. This means that an enlarged failing heart or an overfilled ventricle is less efficient in ejecting blood.

It follows that in an experiment evaluating cardiac function or the effect of interventions, such as anemia and transfusions, all but a single variable should be controlled because of the interdependence of these factors.

In the heart, unlike other organs, tissue hypoxia (and anoxia) will eventually occur if O_2 delivery is permitted to decrease to a level at which tissues no longer have enough O_2 to meet metabolic demands. From equations [1] and [3], it is apparent that tissue hypoxia may be caused by decreased O_2 delivery due to decreases in either [Hb] (anemic hypoxia), CO (stagnant hypoxia) or hemoglobin saturation (hypoxic hypoxia). Each of the determinants of DO_2 has substantial physiologic reserves, thereby enabling the human body to adapt to significant increases in O_2 requirements or decreases in 1 of the determinants of DO_2 as a result of various diseases.

In health, the amount of O_2 delivered to the whole body exceeds resting O_2 requirements by a factor of 2 to 4. For example, if we assume a [Hb] of 150 g/L, 99% saturation of hemoglobin with O_2 and CO of 5 L/minute, then O_2 delivery will be 1032 mL/minute. At rest, the amount of O_2 required or consumed by the whole body will range from 200 to 300 mL/minute. A decrease in [Hb] to 100 g/L would result in an O_2 delivery of 688 mL/minute. Despite this 33% decrease in O_2 delivery, there remains a twofold excess of O_2 delivery compared with O_2 consumption. However, a further drop in [Hb] to 50 g/L with all other parameters, including CO, remaining constant will decrease O_2 delivery to a critical level of 342 mL/minute. Under stable experimental conditions, this dramatic decrease in O_2 delivery would not affect O_2 consumption; however, below a critical level or threshold of O_2 (DO_2 [crit]), O_2 consumption will decrease with further decreases in [Hb] (and decreased O_2 delivery).

There is, therefore, a biphasic relation between O_2 delivery and consumption (Fig. 2); an O_2 delivery-independent portion of the relationship above a threshold value, where O_2 consumption is independent of O_2 delivery, and a delivery or supply-dependent portion, where O_2 delivery is linearly related to O_2 consumption. The latter portion of this relationship indicates the presence of tissue hypoxia. Both laboratory and clinical studies have attempted to determine DO_2 (crit). The most rigorous clinical study[17] found a threshold value of 4 mL/min per kilogram, whereas other clinical and laboratory studies found values in the range of 6–10 mL/min per kilogram.[17–20]

DO_2 measured for the whole body is a composite for all organs, whose individual anaerobic thresholds may be significantly different from the average DO_2 (crit). In addition, the anaerobic threshold and associated DO_2 (crit) values will also vary substantially with metabolic rate, some disease states and perhaps such complex factors as a patient's age or genetic make-up. In the previous example, blood flow to the whole body as reflected by CO did not increase as would otherwise be expected in anemia.

Once blood is oxygenated, it is distributed to all organs and tissues through the arterial tree. Organ blood flow is controlled by arterial tone in medium-sized vessels, which responds primarily to changes in autonomic stimulation and the release of locally generated vasodilating substances. Within organ systems, RBCs are carried into a network of capillaries where O_2 is released to the tissues through the thin walls. Once released, O_2 diffuses through the interstitial space, finally finding its way into cells and their mitochondria to be used in cellular respiration. Each of these physiologic mechanisms may be altered in disease states.

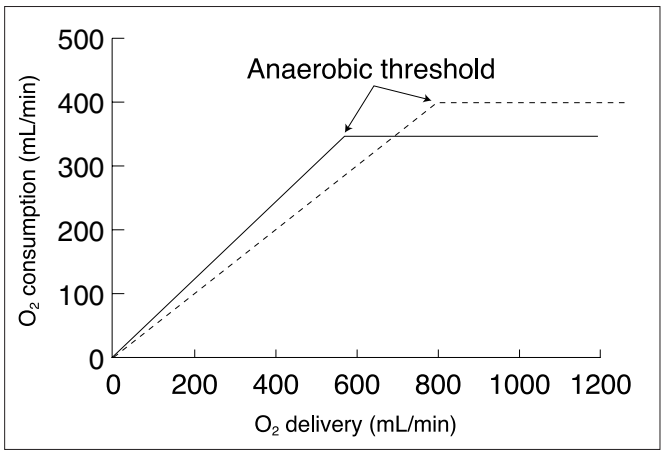

Fig. 2: The biphasic relation between O_2 consumption and O_2 delivery. The dashed line illustrates the postulated changes in the relation in the presence of diseases such as sepsis or adult respiratory distress syndrome. The anaerobic threshold is shifted to the right suggesting that patients require increased levels of delivery to avoid ongoing ischemic damage to vital organs.

Adaptive mechanisms in anemia

In anemia, O_2 carrying capacity is decreased but tissue oxygenation is preserved at [Hb] well below 100 g/L. Adaptive responses include a shift in the oxyhemoglobin dissociation curve, hemodynamic alterations and microcirculatory alterations.

The shift to the right of the oxyhemoglobin dissociation curve in anemia is primarily the result of increased synthesis of 2,3-diphosphoglycerate (2,3-DPG) in RBCs.[21–34] This enables more O_2 to be released to the tissues at a given PO_2, offsetting the effect of the reduced O_2 carrying capacity of the blood. This shift also occurs in vitro with decreases in temperature and pH.[35] Because measurements of hemoglobin O_2 saturation are generally performed on arterial specimens processed at standard temperature and pH, they will not reflect O_2 binding affinity and unloading conditions in the patient's microcirculatory environment, which may be affected by temperature, pH and a number of disease processes. The shift in the oxyhemoglobin dissociation curve because of decreases in pH (increase in hydrogen ion concentration) is referred to as the Bohr effect.[35,36] Because changes in pH rapidly affect the hemoglobin molecule's ability to bind O_2, this mechanism has been postulated to be an important early adaptive response to anemia.[37] However, the equations describing the physical process indicate that a very large change in pH is required to modify the P_{50} by a clinically important amount (i.e., about 10 mm Hg). As a result, the Bohr effect is unlikely to have important clinical consequences.[35,36]

Several hemodynamic alterations also occur following the development of anemia. The most important determinant of cardiovascular response is the patient's volume status or more specifically, left ventricular preload. The combined effect of hypovolemia and anemia often occur as a result of blood loss. Thus, acute anemia may cause tissue hypoxia or anoxia through both diminished CO resulting in stagnant hypoxia and decreased O_2 carrying capacity (anemic hypoxia).[1,3–5] The body attempts to preserve O_2 delivery to vital organs primarily by redistributing the available cardiac output through increased arterial tone. The adrenergic system plays an important role in altering blood flow to and within specific organs. The renin–angiotensin–aldosterone system is also stimulated to retain both water and sodium. Losses in blood volume of 5% to 15% result in variable increases in resting heart rate and diastolic blood pressure. Orthostatic hypotension is often a sensitive indicator of relatively small losses in blood volume that are not sufficient to cause a marked blood pressure fall in the supine position. Larger losses will result in progressive increases in heart rate and decreases in arterial blood pressure accompanied by evidence of organ hypoperfusion. The increased sympathetic tone diverts an ever decreasing global blood flow (CO) away from the splanchnic, skeletal and cutaneous circulation toward the coronary and cerebral circulation. Once vital organ systems such as the kidneys, the central nervous system and the heart are affected, the patient is considered in hypovolemic shock. Although the American College of Surgeons' Committee on Trauma[38] has categorized the cardiovascular and systemic response to acute blood loss according to degree of blood loss, many of these responses are modified by the rapidity of blood loss and patient characteristics such as age, comorbid illnesses, pre-existing volume status and [Hb], the use of medications having cardiac (i.e., beta blockers) or peripheral vascular effects (i.e., antihypertensives).

The compensatory changes in CO have been the most thoroughly studied cardiovascular consequences of normovolemic anemia. When intravascular volume is stable or increases following the development of anemia, increases in CO have been consistently reported. Indeed, an inverse relation between [Hb] and CO has been clearly established in well-controlled laboratory studies (Fig. 3).[37,39–44] An attempt is made to control intravascular volume in most studies. However, there was insufficient information in these reports to ascertain whether the investigators were successful in controlling relevant factors, such as venous tone and total blood volume. Similar clinical observations were made in the perioperative setting[45–52] and in chronic anemia.[39,53–55] Unfortunately, the strength of inferences from clinical studies is limited by confounding factors arising from major comorbid illnesses such as cardiac disease, lack of an appropriate control group and significant weaknesses in study design. Researchers have also attempted to determine the level of anemia at which CO begins to rise. Reported thresholds for this phenomenon have ranged from 70 to 120 g/L.[37,39,56–59]

Two mechanisms are thought to be principally responsible for the physiologic processes underlying increased CO during normovolemic anemia: reduced blood viscosity and increased sympathetic stimulation of the cardiovascular effectors.[1,42,60–62] Blood viscosity affects both preload and afterload, two of the major determinants of CO[60,63,64] whereas sympathetic stimulation primarily increases heart rate and contractility. Compared with hypovolemic anemia, in compensation for normovolemic anemia, the effects of blood viscosity appear to predominate.[63–65]

The interactions between blood flow, blood viscosity and CO are complex. In blood vessels, blood flow affects whole blood viscosity and in turn, blood viscosity modulates CO. Under experimental conditions, blood flow in a rigid hollow cylinder is directly related to the 4th

power of the diameter and the driving pressure and inversely related to the cylinder length and blood viscosity (Poiseuille-Hagen Law).[1,60,61] Also, blood viscosity will increase as flow decreases because of increasing aggregation of RBCs. Thus, viscosity is highest in postcapillary venules where flow is the slowest and lowest in the aorta where flow is fastest. In postcapillary venules, a disproportionate decrease in blood viscosity occurs as anemia worsens and, as a consequence, venous return is augumented for a given venous pressure.

If cardiac function is normal, the increase in venous return or left ventricular preload will be the most important determinant of the increased CO during normovolemic anemia. The conclusion is based on experiments in which viscosity was maintained during anemia using high viscosity colloidal solutions. In such studies,[63] the cardiovascular effects were attenuated compared with similar levels of hemodilution accompanied by reduced whole blood viscosity. Decreased left ventricular afterload, another cardiac consequence of decreased blood viscosity, may also be an important mechanism in maintaining cardiac output if ventricular function is impaired.[63]

Investigators[42,57,63,64,66–68] have also noted alterations in sympathetic stimulation. Anemia causes an increase in heart rate.[37,60,69] This physiologic response is thought to be predominantly mediated by aortic chemoreceptors[42,62] and release of catecholamines.[42,43,66,70,71] However, primary laboratory studies[71,72] and studies of perioperative normovolemic hemodilution[45–47] and chronic anemia[53,54] have not consistently demonstrated significant increases in heart rate in response to moderate degrees of anemia. A detailed review[60] indicated significant differences in species response as well as differences between awake and anesthetized patients. Anesthesia and mechanical ventilation may have significant effects on sympathetic tone, left ventricular loading conditions and contractility. Therefore, the presence of anesthesia and various anesthetic techniques will confound assessments of the relation between heart rate and anemia. Three poorly controlled studies in children did not agree on the contribution of tachycardia[54,73] and stroke volume[74] to the increase in CO.

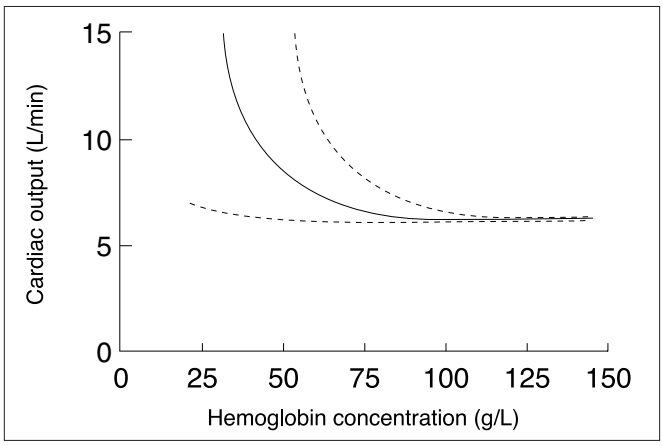

Fig. 3: The theoretical effect of hemoglobin concentration ([Hb]) on cardiac output. The solid curve describes this relation in a healthy adult. The upper dashed line shows how the cardiac output response may be accentuated in a young athlete; the lower dashed line might correspond to poor cardiovascular function.

In summary, the anemia-induced increase in CO is more dependent on stroke volume and, to a lesser extent on heart rate, in most clinical settings. If increased heart rate occurs following normovolemic anemia, one of its major consequences will be to inhibit coronary blood flow by shortening diastole when the left ventricular myocardium is perfused.[75,76] The shortening of diastolic filling time alone is usually insufficient to induce myocardial ischemia in normal subjects. However, the combined effects of decreased diastolic time and anemia may have significant consequences in the presence of coronary artery disease. The O_2 supply–demand relation may also be adversely affected by additional changes to ventricular loading conditions.

Sympathetic stimulation may also affect CO by enhancing myocardial contractility[77,78] and increasing venomotor tone.[42,79] The effects of anemia on left ventricular contractility in isolation have not been clearly determined, given the complex changes in preload, afterload and heart rate. Only one before-and-after hemodilution study used load-independent measures of increased left ventricular contractility.[78] Chapler and Cain[42] have summarized several well-controlled animal studies indicating that venomotor tone is increased and that it results from stimulation of the aortic chemoreceptors. If sympathetic stimulation is significant in the specific clinical setting, then contractility will be increased from stimulation of the beta-adrenergic receptors.[60,66,68,77]

Under laboratory conditions, several investigators[70,80–84] have observed significant increases in coronary blood flow directly related to the degree of normovolemic anemia. These studies do not demonstrate significant shifts in the transmural distribution of coronary flow between endocardium and epicardium in the normal coronary circulation during moderate degrees of anemia. Further, significant alterations in the distribution of flow between major organs following acute hemodilution have also been documented.[37,42,65,72,80,84–88] Disproportionate increases in coronary and cerebral blood flow occurred with simultaneous decreases in blood flow to the splanchnic circulation.

The inverse relation between CO and [Hb] has led investigators to try to find the [Hb] at which O_2 trans-

port is maximum. In a canine model, Richardson and Guyton[89] established that optimum O_2 transport occurred at a hematocrit of 40% to 60%; others[80,84,90] have determined that maximum O_2 delivery occurs at the low end of this range (40%–45%). However, one of the most widely quoted studies[59] found that peak O_2 transport occurred at a hematocrit of 30% ([Hb] 100 g/L). Unfortunately, global indices of optimum O_2 delivery will mask any differences in blood flow between specific organs.[65,70,91,92] In addition, attempting to identify a single [Hb] that maximizes O_2 delivery overlooks the large number of factors interfering with adaptive mechanisms in anyone other than healthy young patients with anemia. None of the identified studies defined optimal hematocrits under experimental conditions that emulate various disease states potentially affecting O_2 demand.

Will the transfusion of allogeneic RBCs reverse any adaptive response to acute or chronic normovolemic anemia? If O_2 carrying capacity is not impaired during RBC storage and hematocrit is restored following a transfusion, the cardiovascular consequences can be expected to be reversed assuming there has been no irreversible ischemic organ damage. However, the storage process alters the properties of RBCs, which may impair flow and O_2 release from hemoglobin[21,26] in the microcirculation.

Microcirculatory effects of anemia and red blood cell transfusions

At the level of the microcirculation, 3 mechanisms may increase the amount of O_2 supplied to tissues by capillary networks. In a model of the microcirculation proposed by Krogh,[93,94] O_2 supply to the tissues may be enhanced through recruitment of previously closed capillaries, increased capillary flow and increased O_2 extraction from existing capillaries. The degree of anemia, the specific tissue bed and a variety of disease processes may affect microcirculatory blood flow and O_2 supply.[1,95,96] As the degree of hemodilution increases and [Hb] decreases, blood viscosity decreases disproportionately in capillary networks. This results in progressive increases in the rate of flow of RBCs through capillaries and proportionate decreases in the time red cells spend in capillaries.[97]

With moderate degrees of anemia, the increased rate of flow may increase the amount of O_2 delivered to tissues.[1] However, during profound anemia, the transit time may be so brief that it interferes with the diffusion of O_2 to cells.[98,99] Indeed, increases in flow rate may be one of the important reasons for the onset of anaerobic metabolism. Although the effect of [Hb] (or hematocrit) on systemic O_2 transport in the central circulation has been well studied, it remains unclear how a higher hematocrit influences O_2 delivery in the microcirculation.[100–102] Until recently, it has been difficult to obtain in situ measurements of blood viscosity, microcirculatory flow, O_2 delivery and cellular respiration,[103] although studies[97,102,104,105] have suggested that microcirculatory stasis and impaired O_2 delivery to the tissues may be directly related to changes in hematocrit. Some theorize that normovolemic hemodilution improves microcirculatory flow and O_2 delivery; others have suggested that hematocrit has limited effects on microcirculatory flow.[106,107]

Transfused RBCs stored in acid-citrate dextrose or citrate-phosphate dextrose may also have different properties than in vivo cells. Many changes tend to be related to the duration of storage. Older units of packed RBCs have lower levels of 2,3-DPG, a small molecule that alters the affinity of hemoglobin for O_2.[21,26,37,72,108–114] Low levels of 2,3-DPG induce a leftward shift in the oxyhemoglobin dissociation curve that may impede delivery of O_2 to the tissues. In addition, storage may alter the characteristics of RBC membranes, decreasing their deformability.[115,116] As a consequence, transfused cells may impair flow in the microcirculation[117] and have a limited ability to release O_2 to tissues. However, storage lesions may be reversible within 24 to 48 hours.

Reports[116,118–121] suggest that disease processes such as sepsis also impair RBC deformability. In conjunction with significant systemic microcirculatory dysfunction, the decrease in RBC deformability may dramatically affect tissue O_2 delivery in sepsis and septic shock.[116,118–120] This body of evidence suggests that transfusion of packed RBCs increases systemic O_2 delivery but may have adverse effects on microcirculatory flow.

Interaction between pathophysiologic processes and anemia

A number of diseases that affect either the entire body or specific organs may limit adaptive responses to anemia. Heart, lung and cerebrovascular diseases have been proposed to increase the risk of adverse consequences from anemia.[37,122,123] Age, severity of illness and therapeutic interventions may also affect adaptive mechanisms.

The heart, especially the left ventricle, may be particularly prone to adverse consequences of anemia, because the myocardium consumes 60% to 75% of all O_2 delivered to the coronary circulation.[70,80–84,90,124] Such a high extraction ratio is unique to the coronary circulation. As a result, O_2 delivery to the myocardium primarily increases by increasing blood flow.[90,125,186–189] Moreover, most of left ventricular perfusion is restricted to the di-

astolic period, and any shortening its duration (e.g., in tachycardia) constrains blood flow. Laboratory studies[43,81,84,90,124–128] of the effects of normovolemic anemia on the coronary circulation reveal minimal consequences from anemia ([Hb] around 70 g/L) if coronary circulation is normal.[44,78,81,90,125,129] However, myocardial dysfunction and ischemia occur earlier or are more significant in anemic animal models with moderate to high grade coronary stenoses compared with controls with normal [Hb].[124,126–131] The degree of experimental control of variables potentially affecting myocardial O_2 consumption was very limited. Only 1 study[186] maintained left atrial pressure and 3[187–189] controlled perfusion pressure in a separately perfused coronary artery.

The clinical data do not appear to be as consistent. Several studies of patients with coronary artery disease undergoing normovolemic hemodilution do not report an increase in cardiac complications or silent ischemia during ECG monitoring.[51,132–135] In addition, a retrospective analysis involving 224 patients undergoing coronary artery bypass grafting was not able to demonstrate a significant association between the [Hb] and coronary sinus lactate levels (an indicator of myocardial ischemia).[136] In 2 recent cohort studies, moderate anemia was poorly tolerated in perioperative[137] and critically ill patients[138] with cardiovascular disease, confirming observations made in the laboratory. Anemia may also result in significant increases in morbidity and mortality in patients with other cardiac pathologies including heart failure and valvular heart disease,[130] presumably because of the greater burden of the adaptive increase in CO.

During normovolemic anemia, cerebral blood flow increases as [Hb] decreases. Investigators have observed increases ranging from 50% to 500% of baseline values in both laboratory studies[139–145] and in one human study.[146] Increased cerebral blood flow occurs because of overall increases in CO, which is preferentially diverted to the cerebral circulation. Also, as O_2 delivery begins to decrease, cerebral tissues extract more O_2 from the blood. A number of factors, including the degree of hemodilution, the type of fluid used for volume expansion and the volume status (preload) and the extent of the cerebrovascular disease, can modify global or regional cerebral blood flow during anemia.[147,148]

The increase in global cerebral blood flow combined with the possibility of improved flow characteristics across vascular stenoses (improved rheology of blood because of decreased viscosity) prompted a number of laboratory and clinical studies[149–154] investigating hemodilution as a therapy for acute ischemic stroke.[143,145,149,155–157] The laboratory studies suggest that moderate degrees of anemia alone should rarely result in or worsen cerebral ischemia. As a therapy in acute ischemic stroke, hemodilution did not produce a significant overall improvement in clinical outcome. However, because of the large variety of variables that may affect the extent of clinical outcomes, the negative findings may not rule out the possibility of therapeutic benefits. Cerebrovascular disease does not appear to predispose patients to significant ill consequences from anemia.

Changes in O_2 delivery to the brain (as a result of increases or decreases in blood flow) during normovolemic anemia do not uniformly affect various forms of cerebral pathologies. For example, patients with increased intracranial pressure from traumatic brain injury may be adversely affected by increased cerebral blood flow. However, following subarachnoid hemorrhage, mild degrees of normovolemic or hypervolemic anemia may improve overall O_2 delivery, possibly by overcoming the effects of cerebral vasospasm, thereby improving cerebral blood flow through decreased viscosity.[158–161] The effects of moderate to severe anemia in subarachnoid hemorrhage have not been assessed either in laboratory or clinical studies.

Redistribution of CO to the coronary and cerebral circulation during normovolemic anemia results in a shunting of blood away from other organs including the kidneys and bowel. In critically ill patients who are affected by a wide variety of pathologic processes this redistribution may result in increased gut ischemia, bacterial translocation and multisystem organ failure.[5,19,162,163] Critical illness may also tax many of the body's adaptive responses, specifically, cardiac performance[164,165] which may already be responding to increased metabolic demands. Pathologic processes affecting the microcirculation, which are particularly prevalent in this population, may also affect the patient's response to anemia and transfusions.

Red blood cell transfusion and O_2 kinetics

We identified 13 studies (Table 4) that have evaluated the impact of RBC transfusions on O_2 kinetics. O_2 delivery uniformly increased but O_2 consumption was observed to change in only 5 of the studies. The lack of change in O_2 consumption reflects either methodologic errors[166] or patients with an elevated anaerobic threshold, rather than indicating that additional RBCs were unnecessary as suggested in 1 study.[167] Even though a number of clinical trials[168–170] have attempted to define optimum levels of O_2 delivery, there is still no consensus on which patients are most likely to benefit and which intervention or approach is superior (i.e., fluids, RBCs, inotropic agents or a combination). The results of a recent meta-analysis suggest greater benefit in perioperative patients.[171] However, all experimental protocols

maintained [Hb] above 100 g/L and, therefore, did not compare various RBC transfusion strategies.

Conclusion

This systematic review of the experimental and clinical evidence revealed that 56% of all studies were well designed and described significant adaptive responses to anemia. The most important adaptive responses involved the cardiovascular system; they consisted of increased CO and a redistribution of blood flow toward the coronary and cerebral circulations and away from the splanchnic vascular beds. The evidence for these physiological responses, especially that from studies that per-

Table 4: Summary of 13 studies of the effects of red blood cell transfusion on O_2 delivery, O_2 consumption and lactate levels

Study	Condition in study population	No. of patients	Average volume of transfusion	Changes after transfusion				Comments
				↑ [Hb]	↑ DO_2	↑ VO_2	↓ Lactate	
Ronco et al[172] (1990)	PCP	5	1.5 U	Yes	Yes	Yes	NA	All patients had ↑ lactate at baseline. Thermodilution used for DO_2 and VO_2 measurements.
Fenwick et al[173] (1990)	ARDS	24	1.5 U	Yes Yes	Yes Yes	No No	No Yes	Normal lactate group (n = 1) was compared with high lactate group (n = 13). Thermodilution catheter used for all measurements. Significant increases in VO_2 in response to transfusion in high lactate group.
Ronco et al[174] (1991)	ARDS	17	1.5 U	Yes	Yes	No	NA	Normal lactate group (n = 7) was compared with high lactate group (n = 10). No relationship between VO_2 and DO_2 when VO_2 directly measured with expired gases.
Shah et al[175] (1982)	Post-trauma	8	1 or 2 U	Yes	Yes	Yes	NA	Thermodilution used for DO_2 and VO_2 measurements.
Steffes et al[176] (1991)	Postoperative + post-trauma	21	1–2 U	Yes	Yes	Yes	No	27 measurements sets in 21 patients. Thermodilution used for DO_2 and VO_2 measurements. Increased lactate levels did not predict VO_2 response.
Babineau et al[167] (1992)	Postoperative	31	328 ± 9 mL	Yes	Yes	No	NA	32 of 33 transfusions were single units. Thermodilution used for DO_2 and VO_2 measurements. 58% of transfusions did not increase VO_2.
Gilbert et al[177] (1988)	Septic	17	Δ 20 g/L	Yes	Yes	No	No	33 measurement sets in 31 patients. 10 of 17 patients had increased lactate levels. VO_2 significantly increased in high group only.
Dietrich et al[178] (1990)	Medical shock (septic/cardiac)	32	577 mL	Yes	Yes	No	No	36 measurement sets in 32 patients. No change in VO_2 after transfusion. Thermodilution used for DO_2 and VO_2 measurements.
Conrad et al[179] (1990)	Septic shock	19	Δ 30 g/L	Yes	Yes	No	No	Normal lactate group (n = 8) compared with high lactate group (n = 11). No increase in VO_2 with transfusion in either group. Thermodilution used for DO_2 and VO_2 measurements.
Marik et al[115] (1993)	Septic	23	3 U	Yes	Yes	No	No	DO2 measured independently of VO_2. Using gastric tonometry, patients receiving old RBCs developed evidence of gastric ischemia.
Lorento et al[180] (1993)	Septic	16	2 U	Yes	Yes	No	NA	Dobutamine significantly increased VO_2; RBCs did not. Thermodilution used for DO_2 and VO2 measurements.
Mink et al[181] (1990)	Septic shock (2 months–6 years)	8	8–10 mL/kg × 1–2 h	Yes	Yes	No	NA	In pediatric patients, VO_2 did not increase with RBCs. Thermodilution used for DO_2 and VO_2 measurements.
Lucking et al[182] (1990)	Septic shock (4 months–15 years)	7	10–15 mL/kg × 1–3 h	Yes	Yes	Yes	NA	8 measurement sets in 7 patients. Thermodilution used for DO_2 and VO_2 measurements.

Note: PCP = Pneumocystis carinii pneumonia; ↑[Hb] = increased hemoglobin concentration; ↑DO_2 = increased O_2 delivery; ↑VO_2 = increased O_2 consumption; NA = not available; ARDS = adult respiratory distress syndrome.

mitted the control of many variables, is powerful and convincing. However, there is a remarkable lack, in both quality and quantity, of clinical studies of anemia addressing how these adaptive mechanisms may be involved or affected by a variety of disease processes. Variables, such as age and patient population may also have an effect.

For these reasons, it is not possible to offer guidelines on how to increase, maintain or even to determine optimum O_2 delivery in high-risk patients or how transfusion strategies might best be used under these conditions.

From the brief review of physiologic principles and the strong consensus in the literature, it is evident that cardiac function must be a central consideration in decisions about transfusion in anemia, because of the critical role it plays in assuring adequate O_2 supply to all vital tissues. Particular attention must be paid to the possible presence of coronary artery disease. Patients with coronary disease are more likely to require transfusions to improve O_2 delivery. There is little convincing evidence to support the notion that cerebral ischemia is aggravated by anemia or that this can be prevented by improving O_2 delivery through rapid correction of anemia. Consequently, the arguments favouring transfusions in the presence of ischemic heart disease do not appear to apply to occlusive cerebrovascular disease.

Because high-level evidence on the interactions of concurrent diseases and anemia in various patient populations is lacking, an understanding of the physiologic consequences of anemia, and of the diseases is useful but not sufficient to guide transfusion practice in specific complex clinical conditions. Further clinical and experimental investigation is required to support comprehensive clinical practice guidelines for RBC transfusions.

We believe that research should be conducted to elucidate the effects of adaptive responses of anemia in a variety of diseases. Laboratory studies should explore the interaction between anemia, transfusions and disease. Controlled clinical studies should also be conducted. Research is needed to describe the consequences of prolonged RBC storage in supply-dependent conditions, such as septic shock. Finally, further studies assessing the clinical consequences of various transfusion strategies are required to assess the impact of anemia and transfusions. In the meantime, prudent and conservative management, based on awareness of risks and sound understanding of the normal and pathologic physiology must remain the guiding principle.

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