Is there an optimal hemoglobin value in the cardiac intensive care unit?
Ronald S. Freudenberger and Jeffrey L. Carson

Anemia is common in patients admitted to the cardiac intensive care unit. Many unique issues must be considered in the treatment of the anemic cardiac patient. Coronary artery disease and left ventricular dysfunction may significantly increase the risk of anemia. These patients have limited reserve because of a high extraction ratio of oxygen in the cardiac circulation. Left ventricular dysfunction increases the risk of complications from transfusion. Recent observational studies suggest that cardiac patients may benefit from a higher transfusion threshold. However, very few patients with cardiovascular disease have been included in clinical trials comparing high and low transfusion triggers. Experimental data and recent studies in humans suggest that cardiac patients may be intolerant of anemia. Pending definitive clinical trials in cardiac patients, we suggest a more aggressive transfusion trigger (9–10 g/dL) in patients with active cardiac disease. Pulmonary edema may be precipitated by transfusion in patients with left ventricular dysfunction. Large clinical trials are urgently needed to determine optimal transfusion thresholds in patients with cardiovascular disease. Curr Opin Crit Care 2003, 9:356–361 © 2003 Lippincott Williams & Wilkins, Inc.

Introduction

Many patients with cardiac disease have decreased hemoglobin concentrations. Anemia may be particularly detrimental in the cardiac patient with left ventricular dysfunction or with coronary artery disease. In addition, there is often a potential risk of transfusing patients with congestive heart failure and stenotic valvular disease because of the large volume of infusion and the movement of fluid into the intravascular space with blood products. Patients with cardiac disease and anemia who are ill enough to require intensive care are especially challenging. In this article, we review the physiology of anemia and its effect on coronary artery disease, congestive heart failure, and aortic stenosis, and summarize the clinical data on blood management in ICU patients with cardiac disease.

How do the compensatory effects of anemia affect the heart with coronary artery disease and left ventricular dysfunction?

Several hemodynamic alterations occur after the development of anemia. The most important determinant of the cardiovascular response is the patient’s volume status or, more specifically, left ventricular preload (Figure 1). The combined effect of hypovolemia and anemia often occurs as a result of blood loss. Acute anemia may cause tissue hypoxia or anoxia through both diminished cardiac output, resulting in stagnant hypoxia, and decreased oxygen-carrying capacity (anemic hypoxia) [1]. The body primarily attempts to preserve oxygen delivery to vital organs by compensatory increases in myocardial contractility and heart rate as well as increased arterial and venous vascular tone mediated through increased sympathetic discharge. In addition, a variety of mechanisms redistribute organ blood flow. The sympathetic nervous system plays an important role in altering blood flow to and within specific organs.

Supply and demand in coronary artery disease

All organs are predisposed to tissue hypoxia (and anoxia). This will eventually occur if oxygen delivery decreases to a level where it is no longer adequate to meet the metabolic demands of the tissues. Normally, the amount of oxygen delivered to the whole body exceeds resting oxygen requirements by a factor of twofold to fourfold. However, in the coronary circulation the myocardium normally consumes 60 to 75% (extraction ratio) of all oxygen delivered [2–5]. Therefore, there is a limited
reserve in the heart compared with other organs. Autoregulation of coronary blood flow is somewhat unique in comparison with other organs. The arterial tone in medium-size vessels responds to changes in autonomic stimulation and the release of endothelial derived vasodilating substances such as nitric oxide. In response to decreased blood flow, the coronary arteries may autoregulate by vasodilation. As the flow decreases the distal vessel dilates; with increasing degrees of coronary stenosis there is further dilation until the coronary stenosis becomes critical. After exhaustion of autoregulation, ie, vasodilation, a decrease in myocardial blood volume is noted with increasing levels of stenosis [6]. In the presence of moderate to severe coronary stenosis, the coronary arteries are maximally dilated and are unable to increase blood flow by autoregulation for any further decrease in oxygen delivery. In contrast to other organ systems, there is less cardiac reserve in response to anemia. To further compound the limits in flow reserve, the heart rate increases to compensate either for hypovolemia or for decreased oxygen delivery to the myocardium. Tachycardia results in decreased coronary perfusion time and further decreases in diastolic coronary blood flow; further limiting myocardial oxygen supply. Theoretically, the presence of left ventricular hypertrophy may also potentiate the adverse consequences of anemia. Because myocardial perfusion occurs through the epicardium to endocardium route, the greater the distance to traverse, the greater the possibility of subendocardial ischemia.

Laboratory studies have investigated the effects of normovolemic anemia on the coronary circulation [5,7,8]. There appear to be minimal consequences from anemia with hemoglobin levels in the range of 7 g/dL if the coronary circulation is normal [9–12]. However, myocardial dysfunction and ischemia either occur earlier, or are more significant, in anemic animal models with moderate to high-grade coronary stenoses in comparison with control animals with normal hemoglobin values [12]. Human data are inconsistent. Several clinical studies in patients with coronary artery disease undergoing normovolemic hemodilution have not reported any increase in cardiac complications or silent ischemia during electrocardiographic monitoring [12]. In addition, a retrospective analysis involving 224 patients undergoing coronary artery bypass grafting surgery did not demonstrate any significant association between the level of hemoglobin and coronary sinus lactate levels (an indicator of myocardial ischemia) [13]. In two recent cohort studies, moderate anemia was poorly tolerated in perioperative patients and critically ill patients with cardiovascular disease, confirming observations made in the laboratory [14,15]. Thus, tachycardia, impaired vasodilator reserve, decrease reserve for oxygen hemoglobin extraction, and possibly left ventricular hypertrophy are factors that make the heart particularly vulnerable to insults from anemia (Figure 2).

**Supply and demand in heart failure**

Anemia may result in significant increases in morbidity and mortality in patients with other cardiac disease, including systolic and diastolic heart failure, presumably because of the greater burden of the adaptive increase in cardiac output. Many studies of systolic heart failure have suggested that at least half of patients with systolic heart failure are anemic [16–18]. The prevalence and severity of the anemia increases with the severity of heart failure. Also, anemia of any cause may produce congestive heart failure [19]. Vasodilatation caused by the accompanying tissue hypoxia lowers the blood pressure, thus activating the sympathetic nervous system. This causes peripheral vasoconstriction and tachycardia, to maintain blood pressure. This in turn activates the renin-angiotensin-aldosterone system. The high angiotensin II levels further increase renal and peripheral va-

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**Figure 1. Frank-Starling curves**

Frank-Starling curves representing states of normal, increased and decreased cardiac contractility illustrating the relationship between stroke volume (output) and end diastolic volume. The increased contractility curve illustrates a greater increase in pressure per increase in volume as seen in diastic dysfunction.

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**Figure 2. Compensatory effects of anemia**

Compensatory effects of anemia – anemia produces noradrenergic stimulation and activation of the rennin angiotensin system with the resultant changes illustrated below all of which potentiate both heart failure and myocardial oxygen demand.
soconstriction and increase aldosterone production. The resultant reduction in renal blood flow and glomerular filtration rate can cause renal insufficiency and fluid retention. The renal insufficiency thus produced may also cause anemia through reduced erythropoietin production and erythropoietin bone marrow activity. The increased aldosterone further increases the fluid retention. Thus, there is a marked increase in plasma and extracellular volume, which can manifest itself as ventricular dilation and central and peripheral edema [16–19].

Volume in congestive heart failure
Many anemic heart failure patients in the ICU will require transfusion. Transfusion of packed red blood cells will significantly expand intravascular volume and potentially raise intracardiac pressures and cause pulmonary edema. Raised intracardiac pressure changes the point on the Frank-Starling curve and may further decrease cardiac output and potentiate pulmonary edema and other heart failure symptoms.

It is estimated that approximately half of all patients hospitalized with heart failure have systolic dysfunction and half have diastolic dysfunction, relaxation abnormality. These patients tend to have a rapid increase in left ventricular end diastolic pressure with relatively small increases in volume. Transfusion in these patients may rapidly produce pulmonary edema with even small increases in intravascular volume. Left ventricular systolic and diastolic cardiac dysfunction is common in the ICU, as is anemia. These two processes and correction by transfusion may potentiate the symptoms of heart failure.

Aortic stenosis
Moderate to severe aortic stenosis presents particular difficulties in transfusion. These patients often have diastolic dysfunction, left ventricular hypertrophy, and impaired peripheral perfusion as a result of low output and compensatory vasoconstriction.

Clinical studies
Relatively few high-quality clinical studies have evaluated transfusion thresholds in cardiac patients admitted to the ICU. Randomized clinical trials are the best study design to evaluate the efficacy of treatment.

Randomized clinical trials
There are limited clinical data that provide important insights on blood management in ICU patients with cardiac disease (Table 1). The most important study is the Transfusion Requirement in Critical Care trial [20,21]. The 838 volume-resuscitated ICU patients were randomized to either a “restrictive” or a “liberal” transfusion strategy. The “restrictive” group received allogeneic red blood cell transfusions at hemoglobin concentrations less than 7 g/dL (and were maintained between 7 and 9 g/dL), and the “liberal” group received red blood cells at hemoglobin concentration less than 10 g/dL (and were maintained between 10 and 12 g/dL) [18]. The “restrictive” group had lower average hemoglobin levels (8.5 vs 10.7 g/dL) and fewer transfusions (2.6 vs 5.6) compared with the liberal group. The 30-day mortality was slightly lower in the “restrictive” transfusion group (18.7% vs 23.3%) although the finding was not statistically significant (P = 0.11).

Hebert et al. published a subanalysis of 43% of patients with cardiovascular disease [22]. Cardiovascular disease was analyzed in two subsets of patients. Overall cardiovascular disease included all patients with diagnoses related to ischemic heart disease (myocardial infarct, angina, congestive heart failure, and cardiogenic shock), rhythm disturbances, cardiac arrest, other forms of shock, uncontrolled hypertension, and cardiac and vascular surgical procedures such as abdominal aortic aneurysm repair and peripheral vascular surgical procedures. There were 160 patients in the restrictive red blood cell transfusion group and 197 in the liberal red blood cell transfusion group. Average daily hemoglobin concentrations were 8.5 g/dL in the restrictive transfusion group and 10.3 g/dL in the liberal transfusion group. The 30-day mortality rate (23% vs 23%), 60-day mortality rate (26% vs 27%), and hospital mortality rate (27% vs 28%) were nearly identical in both groups. The odds of death, after adjustment for potential confounders, were not significant; the adjusted odds ratio was 1.26; 95% confidence interval, 0.70–2.24.

A second subset of patients with ischemic heart disease (n = 257) was also examined. In the patients with confirmed ischemic heart disease, severe peripheral vascular disease, or severe comorbid cardiac disease, there was a nonsignificant (P = 0.3) decrease in overall survival rate in the restrictive group (26%) compared with the liberal group (21%) (Figure 3).

Several other clinical trials have been performed in ICU patients or those undergoing coronary artery bypass grafting surgery. A recent publication examined the use of erythropoietin in ICU patients but did not examine the outcomes in patients with cardiovascular disease [23]. In a trial of patients undergoing first-time elective coronary artery bypass surgery, 428 patients were randomized to arms with transfusion triggers of 9 g/dL versus 8 g/dL [24]. No differences in outcomes were found between the groups, although the hemoglobin levels were similar and the event rates were very low. In a small study of 39 autologous blood donors undergoing coronary artery bypass surgery, patients were randomized to a “liberal” group, who received transfusions to reach a hematocrit level of 32%, and a “conservative” group, who received transfusions for a hematocrit level less than...
25%. There were no differences in clinical complications or exercise endurance between the two groups.

A meta-analysis was performed combining data from five or more trials that compared restrictive with liberal transfusion strategies in various clinical settings [25, 26]. The aforementioned Transfusion Requirement in Critical Care trial contributed 83% of the information in the meta-analysis of mortality data. Restrictive transfusion triggers were not associated with an increase in mortality.

**Observational studies evaluating transfusion**

Several observational studies evaluated the effect of anemia or transfusion practices on mortality and/or morbidity in patients with a high prevalence of cardiovascular disease. These studies involved patients who were admitted to the ICU or who had a high prevalence of cardiac disease and are summarized in Table 1 [27, 30–32]. The results of these studies varied. The first study evaluated 4470 critically ill patients admitted to six Canadian tertiary level ICUs [27]. The need for transfusion was associated with a higher death rate. The outcomes were better for ICU patients who had received transfusions, especially those with cardiovascular disease. The second study involved 2202 patients undergoing coronary artery bypass graft surgery [29]. Upon admission to the ICU, the patients were divided into three groups on the basis of their hematocrit levels: high (>34%), medium (25–33%), and low (<24%). Patients in the high group were more than twice as likely to have a myocardial infarction compared with the medium group. The third study evaluated 2920 patients undergoing surgery for ischemic heart disease [31]. The patients were divided into three groups based on their hematocrit levels: high (>34%), medium (25–33%), and low (<24%). The patients in the high group were more than twice as likely to have a myocardial infarction compared with the medium group.

### Table 1. Clinical Studies in Patients with Cardiac Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical setting</th>
<th>Subjects</th>
<th>Outcomes</th>
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<tr>
<td>Nelson et al. [31]</td>
<td>Vascular surgery</td>
<td>High-risk patients who had undergone elective infrarenal bypass vascular procedures; Hct &gt;28% compared with 77% with Hct &lt;28% no deaths in either group.</td>
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<tr>
<td>Hebert et al. [27]</td>
<td>Critical care</td>
<td>Critically ill patients admitted to ICU; survivors: Hct &gt;28% compared with 77% with Hct &lt;28% no deaths in either group.</td>
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<tr>
<td>Paone et al. [28]</td>
<td>Cardiac surgery</td>
<td>Patients undergoing isolated CABG; transfusion group: (n = 13), no transfusion group: patients were transfused allogeneic RBC on bypass for low SvO2 (&lt;35%) and transfused postoperatively for Hct &lt;20% or at any Hct level if deemed clinically warranted.</td>
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<tr>
<td>Hogue et al. [32]</td>
<td>Urologic surgery</td>
<td>Patients undergoing radical prostatectomy; Hct &lt;28% group vs. Hct &gt;28% group.</td>
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<tr>
<td>Spiess et al. [29]</td>
<td>Cardiac surgery</td>
<td>CABG; high IHCT &gt;34% group (n = 410), medium IHCT group 25 to 33% (n = 1,544), low IHCT &lt;24% group (n = 248), mean age (± sd) 64.3 ± 10.2 years.</td>
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<tr>
<td>Wu et al. [30]</td>
<td>Myocardial infarction</td>
<td>Myocardial infarction patients 65 years old or older; Transfusion was associated with reduction in 30-day mortality in patients with Hct 5.0 to 33%.</td>
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<tr>
<td>Johnson et al. [36]</td>
<td>Cardiac surgery</td>
<td>Liberal: patients received blood transfusion to achieve a Hct value of 32% so long as autologous blood was available; restrictive strategy: patients received transfusions only if Hct value fell below 25%.</td>
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<tr>
<td>Hebert et al. [21]</td>
<td>Critical care</td>
<td>Liberal patients were transfused with PRBC to maintain Hb concentration at 1.0 to 12.0 g/dL; restrictive: patients were transfused to maintain Hb concentration between 7.0 and 9.0 g/dL.</td>
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<tr>
<td>Bracey et al. [24]</td>
<td>Cardiac surgery</td>
<td>Liberal Hb level received an RBC transfusion &lt;9.0 g/dL; restrictive: received RBC transfusion for Hb level &lt;8.0 g/dL.</td>
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<tr>
<td>Hebert et al. [22]</td>
<td>Critical care</td>
<td>Subanalysis from TRICC trial: patients with cardiovascular disease and ischemic heart disease. Cardiovascular patients 33% 30-day mortality in liberal group; 23% 30-day mortality in restrictive group; Ischemic heart disease 21% 30-day mortality in liberal group; 26% 30-day mortality in restrictive group.</td>
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Hct = hematocrit, IHCT = intensive care unit hematocrit, MI = myocardial infarction, ICU = intensive care unit, TRICC, transfusion requirement in critical care; CABG = coronary artery bypass surgery.
as those in the low group. A third study in patients undergoing cardiac surgery found no difference in clinical outcomes [28]. Another recent large study in European ICUs did not analyze outcomes stratified by cardiovascular disease [33].

A study of the effect of transfusion in patients with acute myocardial infarction provides some insight into transfusion in the cardiac patient [30]. Using Medicare billing data, the admission hematocrit level was correlated with adjusted 30-day mortality in patients with acute myocardial infarction. Patients who received transfusion with hematocrit less than 33% had lower mortality than patients with similar hematocrit who did not receive a transfusion. This study suggests that patients with cardiovascular disease may require higher hemoglobin levels. Two small studies in patients undergoing vascular surgery suggested that patients with cardiovascular disease are less tolerant of anemia [31,32]. More ischemic events were seen in anemic patients in both studies.

The validity of these observational studies is uncertain because the decision to transfuse a patient is often correlated with the illness burden of the patient. Statistical techniques that adjust for differences in comorbidity may not be adequate. Subtle but important differences between patients receiving and not receiving transfusion may not be measured and therefore cannot be controlled for in the analysis. The recent discrepancy between the observational studies and the large clinical trial evaluating hormone replacement therapy emphasize the limitations of nonexperimental study design [34,35]. A similar discrepancy occurred in an observational study and a clinical trial evaluating transfusion thresholds in ICU patients that were performed by the same group [21,27]. Clinical trial data are much more reliable.

Authors' recommendations

No adequately powered clinical trials have examined different transfusion thresholds in the cardiac patient. A subanalysis from one clinical trial did suggest that it may be safe to use lower transfusion thresholds in patients with cardiovascular disease. However, this trial was too small to exclude clinically important differences. Several observational studies confirm animal studies that patients with underlying cardiac disease may be more vulnerable to the consequences of anemia than those without cardiovascular disease. Patients with symptoms from anemia, such as angina, or in the peri-infarction setting should undergo more aggressive transfusion. In asymptomatic patients with cardiovascular disease, the definitive answer to the proper transfusion threshold awaits further trials. Until more data become available, we suggest using a higher transfusion threshold, such as 9 to 10 g/dL. We also urge careful attention to the possibility of precipitating pulmonary edema in the patient with left-sided valvular stenosis or systolic or diastolic dysfunction. Ultimately, careful clinical assessment with thoughtful consideration of risks and benefits should guide the transfusion decision, because no set of guidelines will apply to every patient.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

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32 Hogue CW, Goodnough LT, Monk TG: Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. Transfusion 1998, 38:924–931.


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