

Blood Conservation in Cardiac Surgery: The Virginia Commonwealth University (VCU) Experience

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UNTIL RECENTLY, transfusions were required in more than 50% of all cardiac surgery patients.¹ Cardiac surgery remains responsible for 10% to 20% of all transfusions in the United States.¹ This practice continues despite recent data showing that transfusions are independently linked to increased short- and long-term morbidity and mortality.² The direct and indirect costs of blood products continue to rise, whereas blood shortages are becoming more common and reimbursement for transfusion costs is limited.

Multiple techniques for reducing transfusion in cardiac surgery such as euvoletic hemodilution, cell salvage and reinfusion, and the use of prophylactic antifibrinolytics such as aprotinin have been shown to be effective to varying degrees. However, the most effective strategy for reducing transfusion would be to withhold blood until the critical level for oxygen delivery is approached, thereby reducing unnecessary and possibly deleterious transfusions. The ideal hemoglobin for critically ill surgical patients remains in debate, so transfusion decisions are made not based on evidence but on personal belief about the lowest acceptable hemoglobin level for each particular patient.

Medical technology has not advanced to the point of providing real-time, accurate critical oxygen delivery data. Therefore, health care providers are required to use their training, clinical judgment, and experience to determine which patients are approaching the need for the increased oxygen-carrying capacity provided by red blood cell transfusions. Until this technology becomes available, transfusion practice will continue to be determined by local institutional practice, societal and cultural values, and provider comfort level. This ongoing practice has led to wide variability in transfusion practice, sometimes even within institutions.

Further compounding this problem is the lack of evidence-based research on the safety and efficacy of blood transfusion. Until such studies are available, transfusion practice will have to be decided by the risk/benefit ratio in each specific clinical scenario. Because of modern screening techniques, the infectious risks of transfusion have decreased, but the inflammatory and immunomodulatory risks are becoming more widely recognized. Furthermore, the assumed benefits of transfusion remain not clearly defined in the literature. More often than not, clinicians' decisions to transfuse are based on out-dated and insufficient knowledge of risks and based on "perceived" benefits. The role of blood transfusion as necessary and life saving has come into question.

Exposure of patients to allogeneic transfusion can be minimized or avoided by the use of blood conservation techniques. Techniques used are multiple and varied and cannot be uniformly applied across all situations. Strategies include some combination of drugs, devices, and medical and surgical techniques. Use of these techniques by dedicated personnel on a routine basis is necessary for the creation of a blood-conservation program. Institutional blood-conservation programs require commitment from physicians, specialists, administrators, patients, and hospital staff with multidisciplinary cooperation to be effective.

VCU BLOOD-CONSERVATION PROGRAM

With this in mind, VCU adopted a blood-conservation program in cardiac surgery. This initiative consisted of a comprehensive education and awareness program requiring that all transfusions be limited to appropriate clinical indications, such as evidence of an oxygen-delivery debt, rather than any single "trigger" hemoglobin level. The objective of the program was to reduce unnecessary transfusions and promote cost savings in the area of cardiac surgery blood utilization.

In October 1999, this program and its published blood transfusion clinical practice guidelines were implemented. There were 2 purposes of the program. First, it was designed to reduce blood product and equipment utilization costs. This would be accomplished by relying on physician adherence to published and accepted clinical practice guidelines with protocol-driven decision-making processes in place. Also, the use of costly drugs and equipment such as aprotinin and cell-salvage devices would be scrutinized and limited when advisable.

The second purpose was to maintain current patient outcomes. Recent evidence from the literature showed that a restrictive transfusion strategy was at least as effective as a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.³ In fact, in some subgroups, the restrictive group had lower mortality and fewer cardiac complications. Therefore, the goal was to at least maintain the current level of adverse outcomes and possibly improve them.

METHODS

At the start of the program, a database was established for tracking blood-product utilization and adverse events on all cardiac surgery patients. This database consisted of patient demographic information, perioperative risk factors, intraoperative time milestones, hemoglobin levels at various perioperative times, transfusion data, and morbidity and mortality data.

This program required that all blood transfusions be limited to appropriate clinical indications such as hemodynamic instability in the face of active postoperative hemorrhage or a demonstrated oxygen-delivery debt rather than transfusing to achieve a specific "trigger" hemoglobin level. The blood transfusion clinical practice guidelines that were adopted included the following:

1. Transfusion trigger—determine the need for blood transfusion by evaluating intraoperative hematocrit on bypass based on the patient's oxygen delivery and clinical status. The patient will not

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be transfused with packed red blood cells or autologous blood unless their hematocrit has reached 17% and signs of inadequate oxygen delivery are present. Patients with a history of cerebrovascular disease may require a higher hematocrit.

2. Euvolemic hemodilution will be used before bypass when appropriate.
3. All blood product utilization decisions will be made by an attending physician.
4. Incorporate complete clinical status when making decisions about transfusion—do not rely on a single measure (hemoglobin or hematocrit).
5. Preoperative autologous donation and erythropoietin (Epopen) will be used when appropriate.
6. Heparin dosage usage will be based on a heparin-response curve.
7. Epsilon aminocaproic acid or full-dose aprotinin in all cases where appropriate.
8. Hemoconcentration on cardiopulmonary bypass (CPB) when appropriate.

Other measures used to conserve blood included the following:

1. Minimize autologous blood loss by use of cell-saver devices when indicated, reinfusion of residual pump-circuit volume, ultrafiltration during or immediately after CPB when indicated, meticulous hemostatic surgical technique, blood pressure control, positive end-expiratory pressure, and maintenance of normothermia after CPB.
2. Minimize hemodilution by restricting crystalloid administration and using small pump-prime volumes.
3. Optimize coagulation status by full and sustained rewarming; proper heparin and protamine dosing; use of routine hemostatic drugs when appropriate; and point-of-care, real-time TEG and other laboratory-guided correction of abnormal coagulation parameters.
4. Minimize unnecessary transfusions by adherence to strict transfusion guidelines.

The transfusion guidelines routinely applied to all cardiac surgery patients, except patients with known cerebrovascular disease included the following:

1. Red blood cells
 - CPB—keep Hb >5.0 g/dL using cell saver, then hemodilution blood, and then autologous blood before allogeneic blood
 - Immediately after CPB in the operating room before reinfusion of pump-circuit blood—Hb >5.5 g/dL or clinically symptomatic anemia
 - Postoperatively—Hb >6.0 g/dL or clinically symptomatic anemia
2. Platelets
 - CPB—not indicated
 - Immediately after CPB in the operating room—very severe coagulopathic bleeding in appropriate circumstances and laboratory evidence of platelet dysfunction or thrombocytopenia
 - Postoperatively—chest tube output >300 mL first hour or >100 mL/h for 3 consecutive hours and laboratory evidence of platelet dysfunction or thrombocytopenia
3. Fresh frozen plasma
 - CPB—not indicated except for heparin resistance when recombinant ATIII is unavailable
 - Immediately after CPB in the operating room—very severe coagulopathic bleeding in appropriate circumstances and laboratory evidence of coagulation factor deficiency
 - Postoperatively—chest tube output >300 mL first hour or >100 mL/h for 3 consecutive hours and laboratory evidence of coagulation factor deficiency
4. Cryoprecipitate
 - CPB—not indicated

Immediately after CPB in the operating room—very severe coagulopathic bleeding in appropriate circumstances and laboratory evidence of fibrinolysis

Postoperatively—very severe coagulopathic bleeding in appropriate circumstances and laboratory evidence of fibrinolysis

All adult patients undergoing cardiac surgical procedures since October 1999 were included in the database. For comparison, data from charts of all adult patients undergoing procedures in the preceding 3 years were included as a historical control group.

The statistical analysis of the data involved the following procedures:

1. Agreed-on working definitions of preoperative and postoperative comorbid states with index weighting of each condition
2. Identification of specific outcomes and timeline for assessment
3. Descriptive analyses involving propensity scoring using logistic regression. This procedure is to minimize bias associated with a cohort-type study in which subjects differ in the number and degree of comorbid conditions (covariates) that have the strong probability of influencing outcome regardless of treatment condition assigned. Subjects receiving the treatment of interest (treatment or not) are matched as closely as possible by this method with subjects who have equivalent baseline likelihood of achieving the outcome of interest. Subjects are matched so that they balance on multiple covariates using one scalar score, and then standard analyses are performed to compare the matched sets.
4. Univariate analysis of each variable on outcomes to determine distributional characteristics of outcome and all possible predictor variables.
5. Kaplan-Meier estimation of survival function between treatment groups (preprogram [PRE] v postprogram [POST]) to describe survival to specified points in time and compare survival between treatment groups.
6. Proportional hazards model to evaluate relative risks associated with the most influential predictor variables.

RESULTS

In an analysis of the database, Higgins et al evaluated all patients in the database looking at transfusion rates, resource utilization, costs, and mortality.⁴ The investigators found that implementation of the clinical practice guidelines in 1999 led to significantly reduced red blood cell utilization (13% POST v 42% PRE) and significantly reduced costs per patient (\$148/patient POST v \$327/patient PRE). When analyzed in greater detail, it is clear that the majority of the POST cost savings resulted from decreased cell-salvage device usage (savings of \$111/patient) and decreased blood products (savings of \$45/patient) rather than a decrease in aprotinin utilization (savings of \$20/patient). Univariate analysis revealed that age, history of congestive heart failure, and female sex were associated with higher mortality ($p < 0.007$). Multivariate logistic regression showed that blood transfusion was the single statistically significant variable associated with increased mortality ($p < 0.015$).

The author and coinvestigators at VCU analyzed all adult patients undergoing primary coronary artery bypass surgery through 2001 ($n = 998$). The data included demographic and preoperative risk factors, transfusions, hemoglobin levels at 5 perioperative times, time milestones and lengths of stay, and short-term outcome measures. Demographic data and risk factors were similar between PRE and POST (Table 1). In POST, there were significantly fewer patients with an ejection fraction

Table 1. Demographic Characteristics of VCU Cardiac Surgery Patients

Demographic	PRE	POST
Mean age (years)	60.9 ± 11.1	59.6 ± 11.1
Female (%)	38.3	33.5
EF > 50 (%)	42.9	42.3
EF < 30 (%)	8.3	2.9*
Unstable angina (%)	38	45.8*
DM (%)	32.1	27.9
CHF (%)	24.7	20.1
MI < 30d (%)	26.3	20.7*
CVA/TIA (%)	10.4	10.7
CRF (%)	5.6	3.7
Emergency (%)	5.6	9.4*
Median risk score†	4	4

Abbreviations: EF, ejection fraction, DM, diabetes mellitus; CHF, congestive heart failure; MI < 30 d, myocardial infarction within previous 30 days; CVA/TIA, cerebrovascular accident/transient ischemic attack; CRF, chronic renal failure.

**p* < 0.05.

†EuroSCORE (see reference 5).

<30% and fewer patients with a myocardial infarction (MI) within 30 days of surgery; however, there were significantly more patients with unstable angina and more patients who were considered emergent. When risk factors were computed in a model of risk scoring, both groups had the identical overall risk score.⁵

The researchers discovered that transfusion practice changed after the implementation of the blood-conservation program. Overall blood product transfusions decreased from 79% to 39%. Allogeneic red blood cell transfusions decreased from 35% to 16%. Furthermore, patients who did require blood transfusions were transfused fewer total units of blood. Mean transfusions decreased from 4.8 units per patient to 3.1 units per patient.

Hemoglobin levels were similar between groups until intensive care unit (ICU) arrival, when patients in the POST group had an average of 1.6 g/dL lower hemoglobin level. This significant difference persisted until discharge (Fig 1). There

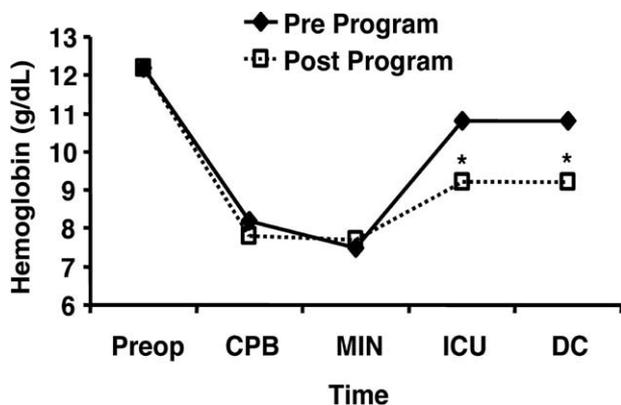


Fig 1. The impact of the VCU blood-conservation program on perioperative hemoglobin levels in cardiac surgery patients. *Indicates significance (*p* < 0.05).

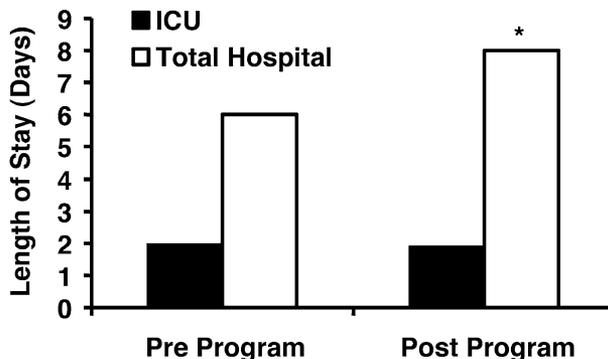


Fig 2. The impact of the VCU blood-conservation program on length of stay in cardiac surgery patients. *Indicates significance (*p* < 0.05).

were no significant differences in time milestones including CPB time, total operating room time, or time to extubation. ICU lengths of stay were similar; however, patients in POST had significantly longer median total hospital lengths of stay (6 v 8 days, *p* < 0.05) (Fig 2).

POST patients required significantly less inotropic support (23.3% v 43.1%, *p* < 0.05), and less often required intra-aortic balloon pump (IABP) support for separation from cardiopulmonary bypass (6.1% v 15.0%, *p* < 0.01). These patients also had a significantly lower incidence of acute renal failure (2.8% v 5.1%, *p* < 0.01) and fewer reoperations for bleeding (2.4% v 5.9%, *p* < 0.05). There were no statistically significant differences in rates of respiratory failure, myocardial infarction, infection, or death (Fig 3).

The author and coinvestigators performed a financial analysis of the data, using published financial models.⁶ Based on 500 patients per year, the authors converted their blood savings into 2002 dollars, taking into account the direct and indirect costs of red blood cell transfusions. Direct costs included fees related to procurement, such as type and crossmatch fees, personnel fees, and the costs of the unit of blood. Indirect costs included the expenses of rare, yet costly, major adverse events such as human immunodeficiency virus, hepatitis, transfusion reactions, and bacterial contamination. Not included in the analysis were costs associated with transfusion-related acute lung injury (TRALI), graft-versus-host disease, ABO-Rh incompatibility, and viral or parasitic diseases. Each unit of red blood cells was estimated to cost \$1422.68. This figure is derived from procurement costs of \$549 per unit and adverse event-related costs of \$873.68 per unit. Based on these figures, estimates of real and potential financial savings were determined. Conservatively, \$569,862 in potential savings was realized from the direct costs of transfusion. When indirect costs of adverse events were included, the potential savings were \$1,432,678 and potentially as high as \$2,371,829 (Fig 4).

DISCUSSION

Based on the results, the blood-conservation program initiated in cardiac surgery at VCU accomplished its goals of cost reduction while maintaining patient outcomes. It is not possible to determine the effect of any one of the blood-conservation

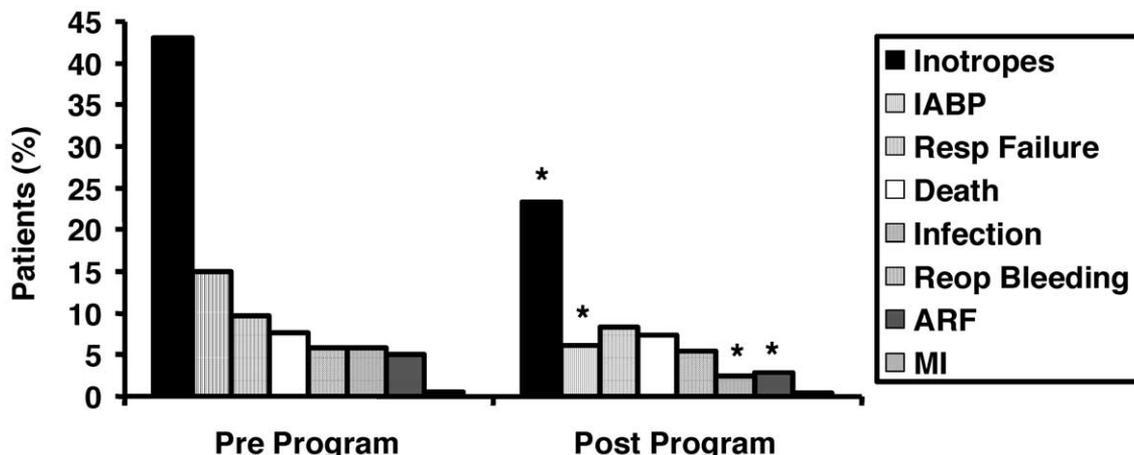


Fig 3. The impact of the VCU blood-conservation program on adverse events in cardiac surgery patients. Resp Failure, respiratory failure; Reop Bleeding, reoperation for bleeding; ARF, acute renal failure. *Indicates significance ($p < 0.05$).

measures used in the program alone. It is likely a combination of multiple strategies and dedicated individuals that contributed to the blood conservation and cost savings that were observed.

The demographic differences observed between PRE and POST are unlikely to have contributed to the differences observed in transfusion and outcome. Because POST had more patients with unstable angina and more patients requiring emergency surgery, it could be expected that these patients were at higher risk and would be more likely to require transfusions and/or more likely to experience adverse events; however, the opposite was observed. Alternatively, this group did have fewer patients with an ejection fraction <30 and fewer patients with a recent MI, which could favor the better outcomes seen in this group. Overall, when risk scores were calculated for the 2 groups, they were found to be the same. Furthermore, because the division between groups was a point in time when the blood conservation program was initiated, any coexisting change in patient population demographics is more likely coincidental and nonsignificant.

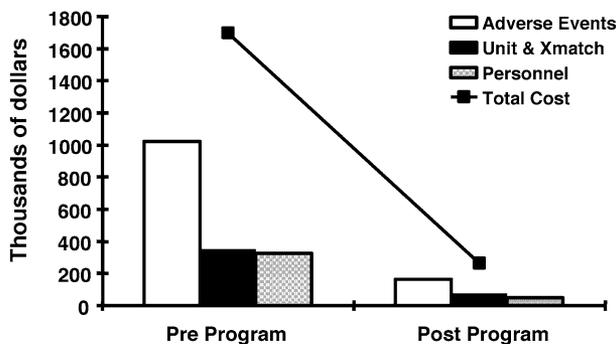


Fig 4. The impact of the VCU blood-conservation program on costs for cardiac surgery patients, based on 500 patients per year. Savings with respect to adverse events (\$863,000), unit and cross-matching (\$295,000), fixed overhead (\$274,000), and total savings (\$1,400,000) were considerable.

Hemoglobin levels observed in the groups followed an expected pattern. The differences in hemoglobin levels when patients entered the ICU can be explained by the change in transfusion practice with the new blood-conservation program. Preprogram, these patients would have been transfused in the post-CPB period, before arrival in the ICU. These differences persisted through discharge, reflecting the change in transfusion practice once patients were in the postoperative period.

One unexpected finding was the significantly longer lengths of stay that were associated with patients in the POST group. Although these patients had significantly lower hemoglobin levels at discharge (9.2 g/dL v 10.8 g/dL, $p < 0.05$), this difference is not likely clinically significant enough to explain the delayed discharge. More likely is the possibility of a shift in physician practice with regard to the timing and suitability of patients for discharge that occurred over the time of data collection.

Patients undergoing cardiac surgery at VCU after implementation of the blood-conservation program experienced no worse outcomes than patients who were historical controls. It could be argued that the decreases in inotropic support, IABP use, and acute renal failure were the result of more advanced perfusion and myocardial protection techniques; however, the basic perfusion and myocardial protection strategies have not changed appreciably for the past decade. If the trend toward less mechanical IABP support was because of more advanced pharmacologic support with better inotropic drugs, an increase would have been expected in the use of inotropes rather than the decrease that was observed. The investigators conclude that the decrease in the use of blood products, which have been shown to be inflammatory in nature and can contribute to complications, resulted in the improved outcomes seen in this group.⁷⁻²⁵

Another significant finding of this study is the significantly decreased rate of re-exploration for bleeding in the blood-conservation group. Re-exploration greatly increases morbidity and mortality.²⁶⁻²⁸ Because of the increased numbers of emergency patients who are at a higher risk for bleeding in the

post-blood-conservation program group, more bleeding problems and reoperations might have been expected in this group.^{20,22} With the absence of a difference in other risk factors for increased bleeding, the investigators concluded that less blood product transfusion led to decreased reoperations for bleeding in these patients.

Previous work by other investigators has shown outcome differences in cardiac surgery related to blood transfusions. Recently, in a landmark study, Engoren et al⁷ studied the long-term survival of cardiac surgery patients. The investigators found that transfused patients had twice the 5-year mortality as nontransfused patients. After correction for comorbidity, transfused patients had a 70% increase in mortality (risk ratio 1.7; 95% confidence interval = 1.4-2.0; $p = 0.001$) compared with those who received no blood transfusions. The authors found that transfused patients were older, smaller, more often female, and had more comorbidities. Multivariate analysis showed that transfusion, peripheral vascular disease, chronic obstructive pulmonary disease, New York Heart Association class IV, and age were all significant predictors of increased long-term mortality. Previous studies of transfusion and shorter-term mortality in coronary artery bypass graft (CABG) patients showed that transfused patients had no better and sometimes worse outcomes within 30 days of surgery.^{8,9} An abstract by Robblee et al¹⁰ showed that anemic CABG patients are not delayed in their recovery at 4 weeks, as measured by functional capacity and quality of life testing, when undergoing a restrictive transfusion strategy for their heart surgery. Studies have shown that multimodal, protocol-driven blood-conservation programs can decrease bleeding and transfusion in a safe and cost-effective manner.¹¹

Several database studies looking at lowest hematocrit at various perioperative times as a marker for outcome showed that lowering the transfusion threshold had no effect on morbidity and mortality.¹²⁻¹⁴ In fact, studies have shown that higher hematocrits may be harmful as shown by increased MIs and increased mortality in women.^{15,16} Furthermore, a randomized multicenter trial in the intensive care unit setting showed that patients with higher hemoglobin levels had an increased risk of death.³ Transfusion of any blood products, including fresh frozen plasma and platelets, has been shown to be an independent predictor of higher 10-year mortality and the number of units given intraoperatively or postoperatively on day 1 has been shown to be a significant predictor of mortality.^{17,18}

Other studies looking at outcomes have shown that the incidence of one or more morbidities in CABG surgery is as

high as 18% to 43%.¹⁹ Studies identifying risk factors for morbidity, mortality, and increased cost identified emergency surgery as a predictor.²⁰ Also, patients requiring emergency surgery were older, female, more likely to have arrhythmias, recent MI, or unstable angina.²¹ Risk factors related to increased blood transfusion include emergency surgery, lower preoperative hemoglobin, higher risk score, more intraoperative blood loss, longer operation time, and type of procedure.²²

The author reported a cost savings associated with the adoption of a blood-conservation program. In the literature, there are several studies looking at costs of blood transfusion. In one study by Collins et al,²³ risk factors that predicted increased length of stay, which is a surrogate marker of cost, included blood transfusion. In another study, the authors determined that autologous donation could be cost-effective when compared with the infectious risks of allogeneic blood transfusions.²⁴ Hannon (unpublished data), in his review of the blood conservation program established at his institution, looked at cost and length of stay, with and without transfusion, in patients undergoing cardiothoracic surgery, major joint surgery, colorectal surgery or patients hospitalized for gastrointestinal hemorrhage or pneumonia. The author's unpublished data (May 2001) showed that transfused patients had an average length of stay of 6.4 days versus 5.5 days in nontransfused patients. Multivariate analysis showed a dose-dependent, linear increase in adverse effects of transfusion including a 2% increase in length of stay per unit transfused and a 2% increase in total cost of hospitalization per unit transfused. The same author reported a 34% decrease in transfusion in the cardiothoracic surgery department after the implementation of a blood-conservation program, which translated to a cumulative cost savings of more than \$5 million.

The effort required to adopt a blood-conservation program and change current practice was enormous. The development and implementation of a program involves a multidisciplinary team of individuals who share a commitment to avoiding allogeneic blood transfusion. The current blood-conservation program in place could be improved by the implementation of several other standard and well-described techniques. For instance, the preoperative management of cardiac surgical patients could be improved to include iron and epogen therapy for anemic patients, better management of antiplatelet and anticoagulant therapies, and less phlebotomy. Intraoperative management could incorporate the use of more topical hemostatic agents and sealants. Ultimately, the use of RBC substitute therapies may become available to provide increased oxygen-carrying capacity without the risks of blood transfusion.

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