Perioperative Blood Management in Cardiac Surgery

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Main Messages

1. Among cardiac surgery centers, transfusion rates vary widely, while overall transfusion risks remain considerable.
2. Transfusion-related lung injury is the number one most frequent cause of transfusion-related death, with transfusion-associated circulatory overload being second.
3. Considerations in perioperative blood management include preoperative blood conservation; intraoperative blood conservation; blood conservation during cardiopulmonary bypass; postoperative blood conservation; intraoperative and postoperative transfusion triggers; and the impact of blood storage duration.

Although cardiac surgery constitutes less than 2% of all surgeries in the United States, patients who undergo cardiac surgery receive approximately 10–15% of the nation's blood each year [1]. Despite the known risks and costs associated with allogeneic transfusions, transfusion rates continue to vary widely among centers that perform cardiac surgery [2]. Recently completed, large, high-quality randomized trials have provided new information that addresses longstanding questions about transfusion in cardiac surgery patients. Two such questions include the ideal hemoglobin trigger for initiating transfusions [3–5] and whether longer duration of blood storage negatively affects outcomes [6]. Furthermore, various methods of blood conservation have been described and refined that dramatically reduce transfusion rates for cardiac surgery. The aim of this chapter is to review evidence-based best practices concerning patient blood management and transfusion therapy in cardiac surgery patients.

Closed cardiac surgery in the early days began with the "blue-baby" operation by Blalock in 1944; however, modern cardiac surgery with a heart-lung machine was first described in the mid-1950s. Transfusion medicine and blood banking also began in the 1940s when methods were discovered that enabled blood to be stored rather than transfused immediately. In the 1970s, when cardiac surgery volumes were increasing, it was recognized that transfusion incurred substantial risks, especially for viral hepatitis. In the early 1980s, the risk of transfusion was compounded by the newly discovered human immunodeficiency (HIV) virus. The years 1983–1984 marked the peak incidence of HIV and viral hep-

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atitis transmission by transfusion. What followed was the era of restrictive transfusion practice, partly related to viral risk, but also supported by several large randomized trials that compared restrictive to liberal transfusion strategies and demonstrated similar outcomes when less blood was transfused [3, 4].

Although improved testing has made the current risk of transfusion-related viral transmission exceedingly low, the overall transfusion risks remain substantial. Transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) represent the number one and number two most frequent causes of transfusion-related death, respectively. Infections (primarily bacterial sepsis from platelets) and hemolytic transfusion reactions were the third and fourth most common causes of fatality according cases reported to the US Food and Drug Administration in 2016 (FDA) (Fig. 23.1) [7]. Over the past decade, primarily driven by patient safety and quality concerns, but also cost effectiveness efforts, we have witnessed the growth of patient blood management programs. Such programs aim to optimize blood utilization in a way that will reduce risks and costs while maintaining or improving outcomes, using methods reviewed in this chapter and described in recent publications [8].

Evidence-Based Methods of Blood Conservation

Preoperative Blood Conservation

The various methods of blood management used for patients undergoing cardiac surgery are listed in Table 23.1. Preoperatively, if time allows, it is important to wait for anticoagulant medication effects to abate before the day of surgery. The advent of direct oral anticoagulant medications and the widespread use of the thienopyridines (e.g. clopidogrel) have challenged cardiac surgeons, as these are widely prescribed by cardiologists for acute coronary events as well as newly inserted coronary stents. The typical patient needs to be off of direct oral anticoagulants for 2–5 days, depending on the medication and the patient's renal function. Patients need between 3 and 5 days for thienopyridines, although both the response to these drugs and the time required for drug-effect resolution are highly variable [9]. Although not yet widespread, preliminary evidence suggests P2Y12 testing to assess recovery

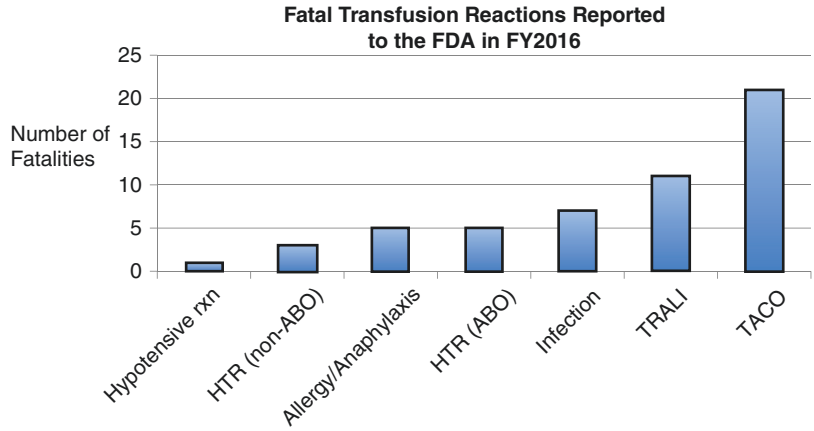

Fig. 23.1 Fatal transfusion reactions reported to the FDA in FY2016. In a report from the Food and Drug Administration (FDA) [9], transfusion-associated circulatory overload (TACO) was the most frequently reported cause of transfusion-related mortality, and transfusion-related acute lung injury (TRALI) was the second most common cause. Infections (bacterial, viral, parasitic), hemolytic transfusion reactions (HTR) from ABO incompatibility, and allergic/anaphylactic reactions were the next most common causes of death; FY16, Fiscal Year 2016

Table 23.1 Methods of blood conservation for cardiac surgery

1.	Education (with emphasis on the RCTs supporting restrictive transfusion)
2.	Creation of transfusion guidelines for all blood components
3.	Decision support for computerized provider order entry (with best practice advisories)
4.	Transfusion guideline compliance audits w/ feedback (reports) to providers
5.	Methods to achieve perioperative blood conservation
	(a) Preoperative anemia management
	(b) Discontinuation of anticoagulants and anti-platelet medications before surgery
	(c) Antifibrinolytics (e.g. aminocaproic acid, tranexamic acid)
	(d) Anesthetic management (autologous normovolemic hemodilution, controlled hypotension, normothermia)
	(e) Point-of-care testing (e.g. viscoelastic testing—TEG or ROTEM)
	(f) Surgical methods (newer cautery methods, topical hemostatics and sealants)
	(g) Hemoconcentrators for pump reservoir blood (MUF, ZBUF)
	(h) Autologous cell salvage
	(i) Evidence-based transfusion triggers
	(j) "Why give 2 when 1 will do" Choosing Wisely® campaign for RBCs
	(k) Reduce phlebotomy blood loss (smaller tubes, eliminate unnecessary testing)

MUF modified ultrafiltration, *RBC* red blood cell, *RCT* randomized controlled trial, *ROTEM* rotational thromboelastometry, *TEG* thromboelastography, *ZBUF* zero-balance ultrafiltration

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of normal platelet function may be useful to determine patient readiness for surgery after discontinuation of these drugs.

Preoperative anemia diagnosis and treatment represents an opportunity to reduce unnecessary transfusions. Iron deficiency anemia is common, and recent studies have shown that patients with heart failure are particularly susceptible [10]. Anemia of chronic disease—recently renamed anemia of inflammation—is also common in elderly patients with chronic conditions. Both of these conditions are treatable, given enough time before surgery, assuming the surgery is not urgent or emergent. Intravenous iron and/or erythropoietin have been used to increase the hemoglobin at a rate of about 1 g per week [11]. Ensuring that patients are diagnosed and treated early enough before scheduled surgery can be challenging even when surgery is non-emergent.

Intraoperative Blood Conservation

Multiple methods of intraoperative blood conservation are available. Autologous blood salvage (cell salvage or autotransfusion) has been an important method of blood conservation for cardiac surgery since the late 1970s when the technology was first introduced. In this procedure, shed blood is collected and washed in a conical-shaped centrifuge bowl to remove debris and concentrate the cells. The final product returned to the patient consists of red blood cells (RBCs) and saline, devoid of any plasma, clotting factors, and platelets. The efficacy of cell salvage for reducing transfusion requirements in cardiac surgery was shown in a meta-analysis by Carless et al. [12] who reported the relative risk of exposure to allogeneic RBCs to be 0.77 and the RBC savings to be 0.68 units per patient. A longstanding belief that cell salvage promotes coagulopathy is based on two premises: residual heparin and dilutional coagulopathy. However, little evidence supports these assertions. First, the amount of residual heparin in salvaged, washed blood is negligible, especially in relation to the amount of heparin administered during cardiopulmonary bypass (CPB). In addition, protamine reversal should neutralize any leftover heparin. Second, the dilutional coagulopathy after salvaged blood should be no different than that which occurs with banked RBCs. The need for plasma and platelets should be considered when approximately 50% or more of the total blood volume has been replaced. Ideally, coagulation testing with a point-of-care, rapid-turnaround result will guide the decision to transfuse plasma and/or platelets, as well as the need for fibrinogen replacement with cryoprecipitate.

Acute normovolemic hemodilution (ANH) has been used despite ongoing debate regarding its effectiveness [13]. This method involves phlebotomy at the beginning of surgery, storage of the

fresh whole blood in citrated anticoagulant, and then dilution of the patient's blood so that when bleeding occurs, fewer red blood cells are lost from the circulation. Based on a recent meta-analysis, ANH does appear to be effective at reducing exposure to allogeneic blood, providing that (1) patients have a high enough starting hemoglobin level; (2) enough blood is removed to allow substantial hemodilution; and (3) enough blood is shed during surgery to make ANH worthwhile. Given the use of cell salvage and hemoconcentration of pump blood, the main benefit of ANH may be the fresh clotting factors and platelets that are given back to the patient at the end of surgery, as the ANH blood is fresh whole blood.

One common cause of excess bleeding during and after cardiac surgery is hypothermia, which impairs coagulation at the level of the clotting cascade and decreases platelet function. Furthermore, coagulation tests such as the INR and the thromboelastogram are routinely run at 37 °C and will come back normal in hypothermic patients, giving a false picture of normal clotting function. Prevention of hypothermia-related bleeding includes use of milder hypothermia during surgery with more local (topical) cardiac cooling rather than systemic cooling, and also more complete rewarming before separation from bypass. However, rewarming at too high a temperature can adversely impact neurologic outcomes by overheating the brain at a time when it is most susceptible to ischemic insults. The completeness of rewarming is typically assessed using a peripheral (bladder or rectal) temperature rather than a true core (blood, esophageal, or nasopharyngeal) temperature. Slower rewarming at a lower blood temperature can result in more complete warming and prevent overheating the vital organs.

Antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid (the lysine analogs) have become almost universally administered during cardiac surgery. Until 2008, aprotinin was the antifibrinolytic of choice, but it was removed from the US market after a randomized trial (the BART trial) [14] reported increased mortality. A longstanding question over effectiveness of antifibrinolytics was addressed in the recent large randomized trial by Myles et al. [15], which showed that tranexamic acid was effective compared to placebo at reducing transfusion requirements (46% reduction) and reoperation for bleeding (1.4% vs. 2.8%); however the incidence of postoperative seizures was increased (0.7% vs. 0.1%). Because seizures appeared to be a dose-related side effect, the dose was reduced by 50% partway through the study. Importantly, the incidence of thrombotic events was not increased by tranexamic acid. Aminocaproic acid is sometimes used to avoid the risk of seizures with tranexamic acid.

Topical hemostatic agents and sealants are efficacious for reducing bleeding during cardiac surgery. Achneck et al. [16] comprehensively reviewed the numerous products that are available, including those most often used in cardiac surgery. Thrombin and gelatin are often mixed together and are also sold as a combination product. Fibrin sealants are also used in cardiac surgery and have shown effectiveness in re-operative cases. Because patients undergoing revision cardiac surgery can require two- to three-fold the amount of transfused blood products, every method of blood conservation becomes critically important [17].

The delicate balance between clotting and bleeding is sometimes a challenge, especially during cardiac surgery. Adding to this challenge is the turnaround time for lab tests, which ideally is short enough to make important clinical decisions on therapy. Typically, the activated clotting time (ACT) is used to determine dosing of heparin and its reversal for patients who require CPB. Since the test result is measured in seconds, and the typical target during extracorporeal support is 400–480, meaningful results take 7–8 min.

Residual coagulation abnormalities occur commonly after reversal of heparin. In such patients, viscoelastic testing can be helpful for diagnosing and treating the bleeding. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are the two primary tests available. These are whole blood clot-

ting tests that yield useful information within 5–10 min (for initiation of clot) or 10–30 min (for clot strength and stability). These tests can help the clinician determine if the coagulopathy is due to clotting factor or fibrinogen deficiency, and they offer quantitative and qualitative information about platelet dysfunction. New variations of these tests that include addition of tissue factor yield more rapid results (1–2 min), especially for clot initiation, which is used to diagnose clotting factor deficiencies.

Clinical studies showing utility for viscoelastic testing in cardiac surgery are limited in number, but in general they support the use of this testing to reduce transfusion requirements, and perhaps even to improve outcomes. A 1999 study by Shore-Lesserson et al. [18] in patients undergoing complex cardiac surgery (e.g. combined coronary artery bypass graft valve, multiple valve, reoperation, or thoracic aortic procedure) used a TEG-based algorithm to determine treatment for microvascular bleeding. The decision to give protamine, plasma, platelets, cryoprecipitate, or antifibrinolytics was determined by TEG results and an algorithm. Use of this algorithm led to decreases in the percentage of patients who required plasma (7.5% vs. 30.8%) and platelets (13.2% vs. 28.8%). The conclusion was that earlier diagnosis and treatment of coagulation abnormalities resulted in earlier hemostasis and a decreased transfusion requirement. In a recent meta-analysis [19] of 15 trials, viscoelastic testing (TEG or ROTEM) reduced overall mortality (RR, 0.52; 95% CI, 0.28 to 0.95), but only eight trials provided data on mortality, and the studies included had a high risk of bias. The viscoelastic testing group had a reduced chance of receiving RBCs (RR, 0.86), plasma (RR, 0.57), and platelets (RR, 0.73), but the risk of reoperation did not decrease. In summary, viscoelastic testing seems to play a valuable role in cardiac surgery and may be useful for more accurately targeting blood component therapy. A TEG-based algorithm that we have been using at Johns Hopkins Hospital to manage post-CPB microvascular bleeding is shown in Fig. 23.2.

Blood Conservation During Cardiopulmonary Bypass

Membrane oxygenators activate the coagulation cascade, dilute platelets and clotting factors, and induce fibrinolysis and systemic inflammatory response syndrome. Various studies have attempted to mitigate these risks with a technique known as modified ultrafiltration (MUF), which has been shown to reduce postoperative blood loss and blood product utilization. MUF involves use of a hydrostatic pressure gradient to remove water and some low-molecular-weight substances from plasma, producing protein-rich whole blood to be returned to the patient after the cessation of CPB. When this technique is used during CPB, it is considered conventional ultrafiltration, or zero-balance ultrafiltration. The ultrafiltration occurs on the arterial side of the pump after blood has been pressurized by the roller pump and gone through the oxygenator membrane. The outlet is connected to the patient's venous line as blood reenters the patient's right atrium after passing through the hemofilter. MUF was created by pediatric cardiac surgeons who were attempting to reduce the hemodilutional effects of CPB, which are particularly pronounced in children but also occur in adults. In a meta-analysis that compared MUF to no ultrafiltration, Boodhwani et al. [20] showed that MUF significantly reduced transfusion requirements. In a prospective randomized trial of 573 patients, Luciani et al. [21] found not only that the mean volume of RBCs transfused for each patient was lower when MUF was used, but also that the proportion of patients who did not receive any blood products was higher (51.8% vs. 38.1%, $P = 0.001$). MUF is a blood conservation strategy that is likely underutilized in adults but has become the standard of care for pediatric cardiac surgical patients.

For zero-balance or conventional ultrafiltration during CPB, and the ultrafiltrate is replaced with an equal volume of balanced electrolyte solution. The zero-balance ultrafiltration filter unit is connected to the CPB pump, takes blood

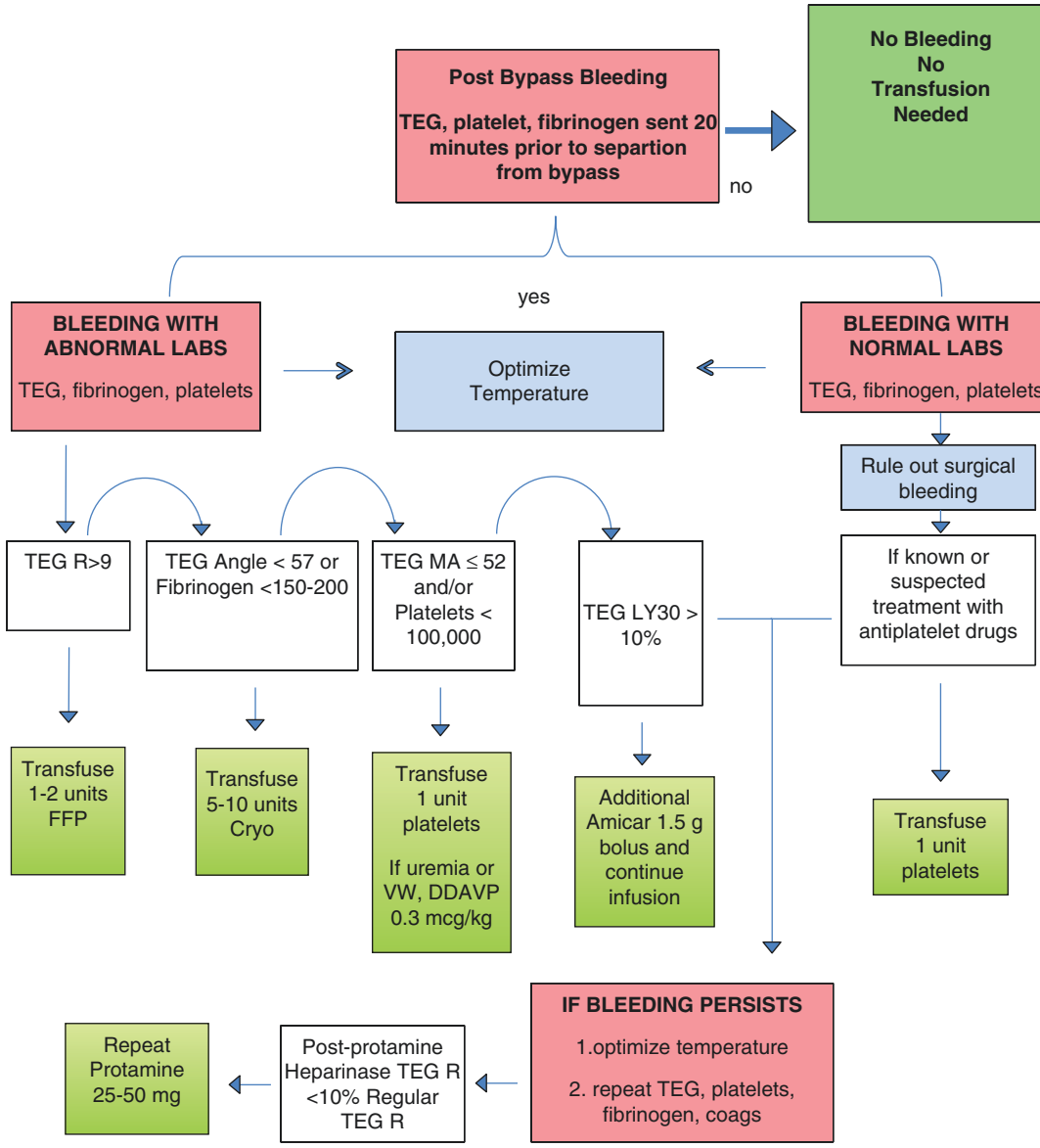

Fig. 23.2 Algorithm for management of microvascular bleeding and transfusion. The Johns Hopkins Hospital TEG-based algorithm for microvascular bleeding. Given the more rapid turnaround time for thromboelastography (TEG) than for traditional coagulation tests (PT, PTT, INR), this algorithm is used to determine therapy for cardiac surgery patients when bleeding persists after cardiopulmonary bypass. It requires a kaolin TEG, heparinase TEG, platelet count, and fibrinogen level

from a pre-membrane port, and runs in parallel to the main cardiopulmonary circuit. To prevent patient blood flow from dropping, the arterial pump rate is increased to compensate for the blood flow through the hemofilter. The main theoretical advantage is that zero-balance ultrafiltration can be used to reduce the inflammatory mediators that are activated when blood contacts a foreign surface. Thus, this technique might decrease lung injury, neurologic inflammation, bleeding, and acute kidney injury, as well as other indicators of morbidity. A recent meta-analysis

showed no significant difference in intensive care unit length of stay, duration of ventilation, chest tube output, or other parameters between patients who received zero-balance ultrafiltration and those who received no hemofiltration [22].

Smaller diameter tubing, shorter tubing length, and low-volume oxygenators can reduce the hemodilution that occurs when patients are placed on CPB. Such low-volume circuits conserve blood and can reduce transfusion requirements. One result, however, is that the pump is moved closer to the surgical field, resulting in less physical space between the operating surgeons and the bypass pump.

Another commonly used perfusion-driven method of blood conservation is retrograde autologous prime (RAP). By using the patient's own venous blood to prime the cardiopulmonary bypass circuit by retrograde flow, hemodilution can be reduced, thereby reducing anemia and transfusion requirements. Typically, the crystalloid used to prime the circuit is pushed out and discarded during the RAP. RAP has been shown to reduce hemodilution and transfusion requirements in both adult and pediatric patients. In one study of adults, RAP reduced hemodilution by 10% (by nadir hematocrit), decreased the percentage of patients who required intraoperative transfusion (from 3% to 23%), and decreased the percentage of patients requiring transfusion during the entire hospitalization (from 27% to 53%) [22].

Postoperative Blood Conservation

Some patients who undergo cardiac surgery require as much transfusion in the postoperative period as they do during surgery. The primary goal postoperatively is to reduce bleeding, which is typically measured by the chest tube output. Excessive or massive bleeding is defined as blood loss of 100–200 mL per hour, on average, for the first 4 h, or more than 2 L in 24 h after surgery. Return to the operating room should be considered when this level of bleeding occurs. Viscoelastic testing often can be used to accurately diagnose the cause of postoperative bleeding; however it will not detect bleeding that results from residual hypothermia as the test is run at 37 °C. Patients are more at risk for bleeding at core temperatures ≤35 °C.

Some centers collect the shed blood from chest and mediastinal drains, which can be transfused with or without cell washing. The transfusion of unwashed blood, however, may incur risk, because such blood is laden with various inflammatory mediators [23]. Furthermore this practice has not been clearly shown to reduce transfusion requirements and has been shown to induce fever, perhaps from an inflammatory reaction.

A particularly concerning problem is the large amount of blood removed from patients for lab testing. Such blood loss from phlebotomy can be substantial, especially for patients in intensive care units, where it can account for more than 60 mL/day. The blood lost includes not only that sent to the laboratory, but also the blood discarded when saline is cleared from the indwelling catheter tubing through which the blood is drawn. In a recent study, it was shown that the average cardiac surgery patient loses 500 mL of blood for lab testing after 10 days in the hospital, and 1000 mL of blood after 20 days [24]. These investigators "were astonished by the extent of bloodletting," with some patients losing a volume of blood equivalent to one to two RBC units [24]. At least three methods can be offered as potential solutions to this problem. First, reduce lab test ordering to those tests that are truly essential, rather than ordering daily blood draws just because the patient is in the hospital. Second, use an in-line blood return device so that the blood drawn to clear the saline from the lines can be returned in a sterile fashion back to the patient. And third, use smaller phlebotomy tubes. Tube volumes vary from 0.5 to 10 mL, or a 20-fold difference. We have switched to pediatric-size tubes throughout most of our hospital (2–4 mL size), rather than adult-size tubes (6–10 mL). The neonatal tubes (0.5 mL) are challenging to use because they do not run through the automated lab machines and must be manually run. Also, because their caps cannot be punctured by a needle, they must be uncapped, which poses a small risk of splash.

The concept of postoperative hemoglobin drift is well recognized. Hemoglobin levels nearly always decrease while patients are hospitalized. This phenomenon is especially true acutely after surgery for four reasons: (1) bleeding continues at varied rates after a patient leaves the operating room; (2) blood is lost through phlebotomy, as described above; (3) hemodilution occurs as a result of intravenous fluid given or fluids that are redistributed into the vascular compartment; and (4) erythropoiesis becomes impaired as a result of surgical stress, which elevates the hepcidin level, a substance critical for mobilizing iron stores for erythropoiesis. Since the body routinely creates and destroys 1% of the red cell mass daily, impaired erythropoiesis predisposes patients to hospital-acquired anemia. After cardiac surgery, hemoglobin levels typically decrease by an average of 1.8 g/dL. The nadir is usually seen on postoperative day three to four, followed by an average increase of 0.7 g/dL over postoperative days 4–10, likely due to hemoconcentration from diuresis [25]. This small but significant upward trend should be considered when using the hemoglobin level to determine need for transfusion.

Transfusion Triggers

Intraoperative Transfusion Triggers

In contrast to the postoperative setting, the ideal intraoperative hemoglobin transfusion trigger for cardiac surgical patients has not been rigorously studied. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines [1] suggest a lower limit of 6 g/dL for patients on CPB with moderate hypothermia, although they recognize that high-risk patients may need higher hemoglobin levels. This recommendation is supported by relatively weak evidence in the guideline. Some centers have begun monitoring cerebral tissue oxygen content with near-infrared spectroscopy technology; however no conclusive evidence shows that this type of monitoring can reliably guide transfusion therapy. By lowering metabolic rate, hypothermic bypass reduces oxygen demands for all vital organs, meaning that lower hemoglobin levels will be tolerated. However, some groups now use either very mild or no systemic hypothermia. Instead they use selective regional cooling of the chest cavity, leaving the brain and kidneys at normal temperature. Additional studies are needed to determine the ideal hemoglobin levels during CPB.

Postoperative Transfusion Triggers

In the past decade, practice has moved toward transfusing less blood to patients, including those undergoing cardiac surgery. This change in practice is supported by one small and three large randomized trials that showed non-inferiority when a restrictive transfusion strategy was compared to a liberal strategy. The three large studies carried out in cardiac surgical patients were the Transfusion Requirements after Cardiac Surgery (TRACS) Trial in 2010 [3], the Transfusion Indication Threshold Reduction (TITRe2) in 2015 [4], and the Transfusion Requirements in Cardiac Surgery (TRICS III) in 2017 [5]. These studies each included postoperative transfusion triggers, and neither demonstrated a difference in the primary outcomes between a liberal and a restrictive transfusion strategy (Fig. 23.3).

TRACS Trial [3]

The TRACS trial enrolled 502 patients and compared restrictive and liberal transfusion triggers (hematocrit 24% vs. 30%, respectively). The primary outcome was a composite of morbidity and mortality, which occurred with similar frequency in the liberal (10%) and restrictive (11%) groups (P = 0.85) (Fig. 23.3).

TITRe2 Trial [4]

The TITRe2 trial compared hemoglobin triggers of 7.5 g/dL (restrictive) and 9.0 g/dL (liberal) in 2007 postoperative cardiac surgery patients. The primary outcome was a serious infection or ischemic event, which occurred with similar frequency in the liberal (33.0%) and restrictive (35.1%) groups (P = 0.30) (Fig. 23.3). The fact

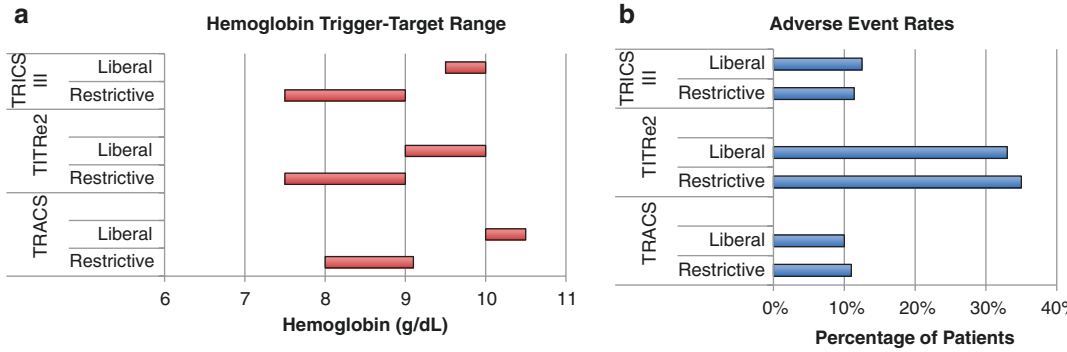

Fig. 23.3 Hemoglobin and primary outcome data are shown for the liberal and restrictive transfusion groups of the TRACS [3], TITRe2 [4], and TRICS III [5] trials. Panel A: The left edge of the red bars represents the hemoglobin trigger (prior to transfusion) for each group, and the right edge represents the hemoglobin target (daily average hemoglobin). Panel B: Among cardiac surgery patients, adverse event rates for the primary outcome (as defined by these trials) were similar (non-inferior) in those assigned to the lower (restrictive) and higher (liberal) hemoglobin transfusion thresholds

that outcome event rates were similar in the two transfusion groups strongly supports use of a restrictive approach, as we only add risk and cost by administering more blood than is necessary. Although the restrictive group in the TITRe2 trial had higher postoperative mortality at 90 days (4.2 vs. 2.6%, P = 0.045), this was a secondary outcome, with no statistical adjustment for multiple comparisons, making the significance questionable. This finding suggests that we may not fully understand tolerable lower levels of hemoglobin in high-risk patients.

TRICS III Trial [5]

The TRICS III trial is the largest randomized trial ever on transfusion triggers, in which over 5000 cardiac surgery patients were randomized to a lower (restrictive) or higher (liberal) hemoglobin trigger (7.5 vs. 9.5 g/dL), starting with induction of anesthesia and continuing in the intensive care unit. On the post-ICU wards, the two groups were treated with triggers of 7.5 vs. 8.5 g/dL. The primary outcome of death, myocardial infarction, stroke, or renal failure requiring dialysis was no different (non-inferior) between groups (restrictive 11.4%, liberal 12.5%). Of interest, this was the one study of the three large trials that included the intraoperative period for these transfusion strategies. Perhaps most interesting is the finding that patients aged 75 or greater had a worse primary outcome in the liberal compared to the restrictive group (14.1 vs. 10.2%; P = 0.004), and one-half of all patients enrolled were in this age group. This is the first time that elderly patients specifically have been shown to do better when given less blood. The other special aspect of the TRICS III study is the 6-month follow-up report [26] on the same primary outcome which was similar in the restrictive (17.4%) and the liberal (17.1%) groups (non-inferior). Hospital readmissions and emergency department visits were also no different between groups. In summary, the TRICS III trial being so large and with longer follow-up, has shown in a fairly conclusive fashion that giving cardiac surgery patients more blood than needed is either unhelpful, or actually harmful to the older patients.

Cleveland Clinic Trial [27]

This trial included over 700 adult cardiac surgery patients randomized to receive less blood (hematocrit trigger 24%) or more blood (hematocrit trigger 28%) from the start of surgery and throughout the hospital stay. The transfusion rate was decreased by 28% in the lower hematocrit group and no differences in morbidity or mortality were reported. The investigators concluded that the risks of anemia and transfusion were

equally balanced within these hematocrit ranges, and that liberal transfusion only added risks and costs without benefit.

A recent meta-analysis [28] of randomized controlled trials involving transfusion triggers reported that restrictive thresholds may place patients at risk for adverse postoperative outcomes. The methods differed from those of other studies in that the authors used a context-specific approach (i.e. they separated groups for analysis according to patient characteristics and clinical settings). Risk ratios (RRs) were calculated for the following 30-day complications: inadequate oxygen supply, mortality, a composite of both, and infections. Thirty-one trials were regrouped into five context-specific risk strata. In patients undergoing cardiac/vascular procedures, restrictive strategies possibly increased the risk of events reflecting inadequate oxygen supply (RR, 1.09; CI, 0.97 to 1.22) and mortality (RR, 1.39; CI, 0.95 to 2.04), and the composite risk of events did reach statistical significance (RR, 1.12; CI, 1.01 to 1.24). Given the limitations of meta-analyses, this finding does not clearly support a liberal transfusion strategy in cardiac surgery patients.

One caveat is that when patients are actively bleeding, they will need to be transfused more liberally because whatever hemoglobin threshold is chosen, transfusion must at least keep pace with the bleeding.

Impact of Blood Storage Duration

RBC storage is an unnatural state during which numerous time-related changes occur, including morphologic and biochemical changes and accumulation of cellular byproducts. Many of these changes are nonlinear [29] and interrelated [30]. The FDA limits storage of RBCs to 42 days based on two requirements: (1) there is less than 1% RBC hemolysis at the end of storage and (2) in vivo RBC survival is >75% at 24 h after transfusion. The 42-day storage limit was not based on RBC product effectiveness or post-transfusion outcomes but has remained unchanged for years.

The Red Blood Cell Storage Lesion

The RBC storage lesion represents changes related to progressive deterioration in the RBC product over storage time. One of the hallmarks of storage lesion relates to changes to RBC morphology. Depending on the duration of storage, RBC units contain varying percentages of normal discocytes, as well as echinocytes and spherocytes. Loss of RBC shape and reduced deformability may contribute to decreased capillary perfusion and increases in aggregation and thrombosis [31]. In response to stress as storage duration increases, RBCs lose membrane integrity secondary to vesiculation processes, with resultant accumulation of microvesicles. Microparticle-encapsulated hemoglobin is of concern clinically because of increased nitric oxide scavenging, potentially leading to reduced tissue oxygenation. Furthermore, older RBC units have a higher free iron content, which may increase non-transferrin-bound iron, predisposing patients to hospital-acquired infections. The storage-related changes in RBCs are outlined in Table 23.2.

Donor phenotypes can contribute to RBCs being more or less susceptible to storage lesion, which may influence RBC survival and the quality of the donor unit. Dumont and Aubuchon [32] reported substantial variability among donors in reference to end-of-storage radiolabeled RBC recovery, which ranged from 35% to 82%. In addition to characteristics of the donor, preservation milieu can influence variability in deterioration of the RBC product. Thus, expiration dates that currently distinguish fresh and old RBC groups may not correspond to metabolic aging patterns during storage. Omics technology could play a future role in better understanding markers for storage-related changes to RBCs.

Clinical Studies on Duration of Storage

Recent controlled trials report similar outcomes in patients randomized to shorter or longer duration of RBC storage in clinical settings of cardiac

Table 23.2 Characteristic changes to red blood cells during storage

Morphologic	Biochemical	Substance accumulation
Loss of shape and membrane integrity	Decreased pH	Increased microvesicles
Membrane loss	Decreased glutathione	Increased inflammatory mediators
Membrane protein and lipid conformational and organizational changes	Decreased S-nitrosohemoglobin (SNO-Hb) bioactivity	Senescent red blood cells
Increased aggregability	Decreased 2,3 diphosphoglycerate	Oxidative stress
Viscoelastic changes	Decreased adenosine triphosphate	Interleukin-8, TNF-alpha, TGF-beta
Oxidative injury to structural proteins, lipids, and carbohydrates	Increased free hemoglobin	Increased reactive oxygen species
Increased population of spherocytes and echinocytes	Increased lactate	Bioactive lipids (activate neutrophils)
Reduced deformability	Increased potassium and sodium	Lipids
Decreased membrane domain	Increased ammonium	Cytokines
Increased band 3 oligomers	Decreased labile proteins: complement, fibronectin, coagulation factors	Complement, anaphylatoxins C3a and C5a
Increased ceramide rafts	Decreased NADH	Membrane attack complexes (MAC)

surgery [33], intensive care [34], and pediatric surgery (Fig. 23.4) [35]. However, it is important to recognize that these trials have different definitions for what constitutes fresh and old RBC units. Furthermore, in vitro aging processes are not necessarily aligned with the fresh and old RBC groupings used in these studies. Bordbar and colleagues [29] identified distinct metabolic states that exhibited nonlinear decay in stored RBCs, suggesting inconsistent cutoffs to define fresh and old RBC units. Of note, these authors asked a more fundamental question: "what is old and what is fresh?"

Mortality was the primary outcome, and results are shown separately for adults and neonates, infants, and children. No significant difference is apparent; however, studies were not allowed to purposefully transfuse blood in the last week or two of the allowed 42-day storage limit (Reprinted from Carson, et al., JAMA 2016;316:2025–35) [6]. Differences in methodology have also been proposed as a reason for inconsistencies in findings between observational and clinical trials on storage duration. For example, RBC units transfused in recent trials were likely not old enough to be used in a proper examination of clinical outcomes after long-term storage (i.e. RBCs at the end of shelf-life, 5–6 weeks storage duration). Other investigators noted that recent clinical trials were underpowered to answer the question of whether prolonged RBC storage (4–6 weeks) is associated with increased mortality [36]. Furthermore, Klein [36] and others at the Clinical Center of the National Institutes of Health now use an upper limit of 35 days for RBC storage, similar to that used in Ireland, Germany, and the UK. The percentage of RBC units transfused after 35 days of storage is reportedly between 9.7% and 20.7%. The most recent recommendations endorsed by the AABB are to continue with current guidelines (i.e. no changes in RBC storage duration limits), or preferentially use fresh RBCs [6].

Extremes of Transfusion

Patient Who Don't Agree to Transfusion

For personal or religious reasons, some patients do not agree to allogeneic blood transfusions. Such patients receive specialized treatment called "bloodless" care [37]. Centers that specialize in

Source	Fresher Blood No. of Deaths	Fresher Blood Total No.	Standard Issue Blood No. of Deaths	Standard Issue Blood Total No.	RR (95% CI)	Weight, %
Adults						
Bennett-Guerrero et al,[33] 2009	1	12	0	11	2.77 (0.12-61.65)	0.1
Aubron et al,[34] 2012	5	25	2	26	2.60 (0.55-12.19)	0.4
Schulman et al,[30] 2002	4	8	2	9	2.25 (0.55-9.17)	0.4
Hebert et al,[32] 2005	5	26	4	31	1.49 (0.45-4.98)	0.6
Steiner et al,[41] 2015	23	538	29	560	0.83 (0.48-1.41)	3.1
Kor et al,[37] 2012	17	50	22	50	0.77 (0.47-1.27)	3.6
Heddle et al,[36] 2012	35	309	61	601	1.12 (0.75-1.65)	5.8
Lacroix et al,[40] 2015	448	1211	430	1219	1.05 (0.94-1.17)	79.2
Subtotal	538	2179	550	2507	1.04 (0.95-1.15)	93.2
Heterogeneity: τ^2=0; χ^2_7=5.47; *P*=.60; I^2=0%						
Tests for overall effect: z score = 0.85; *P*= .40						
Neonates, Infants, and Children						
Dhabangi et al,[38] 2013	1	37	0	37	3.00 (0.13-71.34)	0.1
Strauss et al,[29] 1996	0	21	1	19	0.30 (0.01-7.02)	0.1
Dhabangi et al,[39] 2015	7	143	5	143	1.40 (0.45-4.31)	0.7
Fernandes da Cunha et al,[31] 2005	9	26	10	26	0.90 (0.44-1.85)	1.7
Fergusson et al,[35] 2012	30	188	31	189	0.97 (0.61-1.54)	4.2
Subtotal	47	415	47	414	0.99 (0.69-1.42)	6.8
Heterogeneity: τ^2=0; χ^2_4=1.46; *P*=.83; I^2=0%						
Tests for overall effect: z score = 0.06; *P*= .96						
Overall	585	2594	597	2921	1.04 (0.95-1.14)	100
Heterogeneity: τ^2=0; χ^2_{12}=7.00; *P*=.86; I^2=0%						
Tests for overall effect: z score = 0.81; *P*= .42						
Tests for subgroup differences: χ^2_1 =0.08; *P*=.78; I^2=0%						

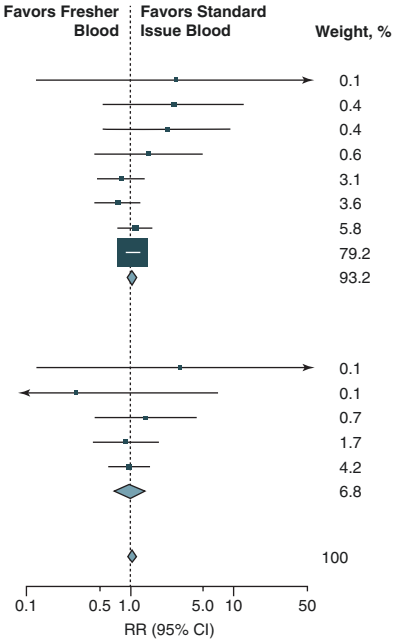

Fig. 23.4 Meta-analysis of randomized clinical trials comparing fresher and standard-issue blood

bloodless medicine are well versed with methods used to ensure good outcomes when blood is not an option. All of the above methods of blood conservation are utilized, starting with aggressive preoperative anemia diagnosis and treatment as outlined in a report by Jassar et al. [38]. Often, intravenous iron and/or erythropoietin are administered preoperatively to increase the red cell mass to a target threshold determined by the patient's body mass. Because smaller patients have a lower total blood volume and thus a lower allowable blood loss, a higher preoperative hemoglobin is targeted. A weekly visit to an outpatient infusion clinic may be required for intravenous administration of iron dextran (1000 mg), along with erythropoietin or darbepoetin. Intraoperatively, meticulous surgical technique is used, and perfusionists play a major role in blood conservation as outlined above. When all blood conservation methods are optimized, these patients who do not accept transfusion do just as well, or better, than patients who accept allogeneic transfusion [39, 40].

Patients Who Receive Massive Transfusion

Transfusion for blood loss that approaches or exceeds one blood volume (10 units) is considered to be a massive transfusion, although the true definition usually involves a time period (typically 24 h). Such patients are likely to require not only RBCs but also plasma and platelets, and the ideal ratio of these blood components is important to consider. The only randomized trial that addressed this ratio was carried out in hemorrhaging trauma victims (the PROPPR Trial) [41]. That study showed no difference in the primary outcome (mortality) at 24 h between the higher and lower plasma- and platelet-to-RBC ratio groups. However, the incidence of hemorrhagic death was higher in the group that received less plasma and platelets, and the investigators interpreted this finding to favor a 1:1:1 ratio of RBCs, plasma, and platelets for massive transfusion. Whether or not these findings apply to non-trauma patients or cardiac sur-

Massive Transfusion Protocol (When to Initiate)

- Loss of entire blood volume within 24 hrs
- 50% of blood volume in 3 hrs
- Ongoing bleeding at ≥150 ml/min
- Rapid bleeding with circulatory failure despite volume replacement

Massive Transfusion Protocol (Procedure)

- Sample for type and screen to blood bank
- Blood products in containers (coolers)
- 1:1:1 ratio of RBC:FFP:Platelets (6 u RBC, 5 u FFP, 1 apheresis unit platelets)
- 10 u Cryoprecipitate in coolers 3, 6, and 9
- Complete use of 1 cooler before next cooler
- Upon issuing a cooler, blood bank prepares next cooler
- 1 cooler every 20-30 min until protocol discontinued

- Labs upon initiation
  type and screen
  CBC
  PT/PTT/INR
  ABG
  Comp Metabolic panel
  iCa
  Lactate
- Labs to send every one hour
  CBC
  PT/PTT/INR
  Fibrinogen
  ABG
  iCa
  Lactate

Fig. 23.5 Algorithm for massive transfusion protocol. The Johns Hopkins Hospital massive transfusion protocol. The ratio of blood components represents a 1:1:1 ratio for red blood cells (RBCs), plasma (FFP), and platelets. An apheresis unit of platelets contains 1 unit of plasma and the number of platelets present in 6 units of whole blood (thus the 6:5:1 unit ratio for RBCs, FFP, and platelets). Although not shown, viscoelastic coagulation testing (thromboelastography, TEG) is recommended to guide the ratio of blood components transfused, when possible

gery is unclear. Ideally, point-of-care or rapid-turnaround lab testing should be used to monitor coagulation and guide the ratio of blood components given. See Fig. 23.5 for the Johns Hopkins massive transfusion protocol.

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