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Management of Intraoperative Fluid Balance and Blood Conservation Techniques in Adult Cardiac Surgery

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ABSTRACT

Blood transfusions are associated with adverse physiologic effects and increased cost, and therefore reduction of blood product use during surgery is a desirable goal for all patients. Cardiac surgery is a major consumer of donor blood products, especially when cardiopulmonary bypass (CPB) is used, because hematocrit drops precipitously during CPB due to blood loss and blood cell dilution. Advanced age, low preoperative red blood cell volume (preoperative anemia or small body size), preoperative antiplatelet or antithrombotic drugs, complex or re-operative procedures or emergency operations, and patient comorbidities were identified as important transfusion risk indicators in a report recently published by the Society of Cardiovascular Anesthesiologists. This report also identified several pre- and intraoperative interventions that may help reduce blood transfusions, including off-pump procedures, preoperative autologous blood donation, normovolemic hemodilution, and routine cell saver use.

A multimodal approach to blood conservation, with high-risk patients receiving all available interventions, may help preserve vital organ perfusion and reduce blood product utilization. In addition, because positive intravenous fluid balance is a significant factor affecting hemodilution during cardiac surgery, especially when CPB is used, strategies aimed at limiting intraoperative fluid balance positiveness may also lead to reduced blood product utilization.

This review discusses currently available techniques that can be used intraoperatively in an attempt to avoid or minimize fluid balance positiveness, to preserve the patient's own red blood cells, and to decrease blood product utilization during cardiac surgery.

INTRODUCTION

Transfusion of blood products is associated with adverse effects and costs. Consequently, reduction of blood transfusions during surgery through preservation of a patient's own red cells has been identified as a relevant, important goal [Goodnough 2003]. Strategies aimed at reducing blood product utilization are particularly important in cardiac surgery, especially when cardiopulmonary bypass (CPB) is used, because concurrent blood loss and red blood cell dilution due to positive fluid balance during CPB result in precipitous hematocrit drop and need for transfusion. Published data suggest that simple behavioral interventions, such as education, transfusion guidelines, transfusion audits, and use of transfusion forms with highlighted transfusion criteria, effectively alter physician transfusion practices and reduce blood utilization [Tinmouth 2005]. In a report by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists [Ferraris 2007], advanced age, low preoperative red blood cell volume (preoperative anemia or small body size), preoperative antiplatelet or antithrombotic drugs, complex or re-operative procedures or emergency operations, and non-cardiac patient comorbidities were identified as important indicators of risk for transfusion. In the same report, careful literature review revealed several simple preoperative and intraoperative interventions likely to reduce blood transfusion; these interventions include use of drugs that increase preoperative blood volume (eg, erythropoietin) or decrease postoperative bleeding (eg, antifibrinolytics), limitation of antithrombotic drugs, selective use of off-pump coronary artery bypass graft surgery (OPCABG), preoperative autologous blood donation, normovolemic hemodilution, and routine use of cell-saving devices. Existing guidelines emphasize the significance of a multimodal approach to blood conservation, with high-risk patients receiving all available interventions under appropriate transfusion algorithms [ASA Task Force on Perioperative Blood Transfusion and Adjuvant Therapies 2006; Ferraris 2007]. Adoption of blood conservation therapies has been slow despite their documented effectiveness [Goodnough 1997; Hutchinson 2001]. Clinical judgement is of paramount importance in evaluating the risk versus benefit of transfusion for each individual patient in an attempt to maintain vital organ perfusion while avoiding unnecessary transfusions [Spiess 2005].

Based on an up-to-date literature review and our own clinical experiences, this review discusses currently available techniques that can be used intraoperatively by anesthesiologists in an attempt to decrease blood product utilization during cardiac surgery.

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METHODS

We searched for original articles, review articles, case series or case reports, and editorials using the MEDLINE database (January 1975 to March 2010), the Cochrane Central Register of Controlled Trials (fourth quarter, 2009), the EMBASE (January 1975 to December 2009), and the reference lists of original and review articles, case series, and case reports, by combining the terms "blood and conservation," "blood and conservation and technique," "blood and conservation and cardiac surgery," and "blood and conservation and technique and cardiac surgery." The search was limited to humans and adults. Publications in languages other than English, publications without an English abstract, and publications without abstracts were excluded, except from case series and case reports, since they usually have no abstract. We used PubMed advanced search and 3 different search strategies: (1) *blood* and *conservation*, 353 results; (2) *blood and conservation* and *technique*, 17 results; and (3) *blood and conservation and technique* and *cardiac and surgery*, 9 results. All identified citations (abstracts, case studies, and case reports that seemed relevant to this review) were independently reviewed by 2 authors (GV and MK). We focused on blood conservation techniques and excluded the use of multiple combinations of drugs. Such techniques exploit appropriate technological devices, surgical, medical, or other specialists' techniques, and an interdisciplinary team approach for the reduction of the use of allogeneic blood transfusion.

RESULTS

The search strategy yielded 379 abstracts, case studies, and case reports for initial consideration. All records were entered into a Reference Manager® v. 12 database (Thomson Reuters, New York, New York, USA), and 78 articles were found to be of relevance. The full text of these 78 original articles, review articles, case series, case reports, and editorials was retrieved and examined by the above authors (GV and MK), and any disagreements were resolved by discussion. Finally, 61 articles were included in this narrative review.

EXTRACORPOREAL CIRCULATION AND HEMODILUTION

Although priming fluid added to the circulation on CPB initiation does not significantly affect circulating erythrocyte mass, it results in acute dilutional anemia, which can be exacerbated by pre-CPB fluid administration. This red blood cell dilution becomes a primary determinant of transfusion, because hemoglobin or hematocrit values are often used as "transfusion triggers" in clinical practice [Paone 1994; DeFoe 2001], even though use of these "transfusion triggers" is not supported by high-level evidence [Herbert 2004; Tinmouth 2005]. We found 14 articles that focus on the safety of hemodilution during CPB (Table 1) [Lowenstein 1981; Cosgrove 1985; Utley 1990; Paone 1994; DeFoe 2001; Karkouti 2001; Engoren 2002; Habib 2003; Swaminathan 2003; Arora 2004; Herbert 2004; Dial 2005; Habib 2005; Tinmouth 2005]. Five of these articles suggest that increased or extreme hemodilution is associated with worse organ dysfunction/injury and increased morbidity [Shinoka 1996; DeFoe 2001; Habib 2003; Habib 2005; Swaminathan 2003]. Eight articles and 1 animal study supports the safety of the increased hemodilution methods during CPB [Lowenstein 1981; Cosgrove 1985; Utley 1990; Paone 1994; Karkouti 2001; Engoren 2002; Arora 2004; Dial 2005; Tinmouth 2005], and 1 article is an editorial and does not support hemoglobin (Hb) < 7 g/dL in the general population [Hebert 2004]. Preoperative Hb 12.0 or less, emergent operation, renal failure, female sex, age 70 years or older, left ventricular ejection fraction 0.40 or less, redo procedure, and low body surface area are independent predictors of erythrocyte transfusion in cardiac surgery according to an internally validated logistic regression risk model. This model is a sensitive and specific predictor of allogeneic blood product use in patients undergoing isolated CABG [Arora 2004]. Utilization of this model and also some other models with similar information allows for preoperative risk stratification and may allow for more rational resource allocation of costly blood conservation strategies and blood bank resources [Cosgrove 1985; DeFoe 2001; Karkouti 2001; Engoren 2002; Arora 2004; Dial 2005]. Blood loss and hemodilution have a greater impact on Hb concentration in female patients and in patients with low body surface area, compared to men with average somatometric values [DeFoe 2001]. Because these observations underline the impact of hemodilution on blood product use, avoidance of hemodilution is an important step toward blood conservation during cardiac surgery [Tempe 2005], and studies evaluating hemodilution during CPB are currently underway (www.clinicaltrials.gov NCT00660608). Hb or hematocrit values are even less appropriate indicators of the need to transfuse in iatrogenic hemodilution cases, where accurate blood loss and intravascular blood volume estimates are difficult or impossible. During CPB, systemic perfusion and oxygenation are provided under conditions of heparinization, hemodilution with reduced blood viscosity, non-pulsatile blood flow, and hypothermia. These conditions significantly alter systemic physiology and formed blood elements [Utley 1990], so oxygen tissue delivery may remain adequate with hematocrit values well below baseline physiologic levels. Consequently, other physiologic variables, such as whole body oxygen-carrying capacity, oxygen consumption, oxygen extraction ratios, and oxygen delivery may be more appropriate indicators of need to transfuse in such cases. Hb values as low as 5.0 g/dL have been shown to provide adequate oxygen delivery during CPB [Lowenstein 1981; Cosgrove 1985]. All the above studies do not exactly support the reduction of blood product transfusions; instead they give us predictive models and information that we can use and reduce blood product transfusions in some patient subgroups. This is very important not only for the reduction of the transfusions cost but also because transfusions may be associated with increased long-term mortality [Engoren 2002].

Although these observations may create a sense of safety and decrease the "transfusion threshold" to lower hematocrit values, other clinical data [Habib 2003; Swaminathan

Table 1. Extracorporeal Circulation and Hemodilution. Predictive models and possible transfusion strategies according to sex, body surface area, age, EO, preoperative Hct, and other comorbities underlie the impact of hemodilution in reducing transfusions.*

Resource	Design	Number of Patients	Aim of the Study	Study Conclusion
DeFoe 2001 (–)	Prospective, feasible trial	6980	Association between nadir hematocrit and in-hospital mortality during CPB	Lowest Hct = increased risk for in-hospital mortality in female patients and in patients with smaller body surface
Paone 1994 (+)	Mainly retrospective trial	947 + 314	2 groups of patients, strict versus usual transfusion strategy	Defined transfusion criteria = safe and effective method for reducing RBC transfusions
Tinmouth 2005 (+)	Review article	19 studies	Simple and multifaceted interventions	Behavioral-simple interventions = effective methods, rigorous designed trial needed
Herbert 2004	Editorial	—	When is RBC transfusion beneficial?	Hb > 7 g/dL in general population and Hb > 8 g/dL in patients with cardiovascular disease
Arora 2004 (+)	Retrospective trial	3046	Logistic regression risk model for prediction of blood product use. Utilization of this model may reduce RBC transfusions.	Predictors of blood transfusion = preoperative Hb ≤ 12.0, EO, renal failure, female sex, age ≥ 70 years, LVEF ≤ 0.40, redo procedure, and low body surface area
Karkouti 2001 (+)	Prospective trial	1007	Logistic regression risk model for prediction and reduction of blood product use	Predictors of blood transfusion = preoperative Hb, weigh, age, sex. Simple and valid prediction rule for predicting the risk of blood transfusion.
Engoren 2002 (+)	Retrospective trial	1915	Effects of transfusion on long-term survival after cardiac operation	Increased long-term mortality
Dial 2005 (+)	Prospective study	613	Risk factors for development: low intraoperative hematocrit level and excessive postoperative bleeding	Limiting risk factors and hemodilution could limit bleeding and reduce blood product transfusions
Utley 1990 (+)	Review	—	Information in complement activation, immune response, anaphylactic reactions, coagulation, and cerebral dysfunction	Increased transfusion requirement = low Hct, female gender, increased age, small body size, low EF, reoperation, and EO
Cosgrove 1985 (+)	Prospective study	441	Determine predictors of blood utilization during myocardial revascularization	Trend for need and amount of transfusion = age, sex, weight, body surface area, preoperative Hct, blood volume, and red blood cell volume
Lowenstein 1981 (+)	Prospective animal study	22 dogs	Hb and CPB	Values ≥ 5.0 g/dL = adequate oxygen delivery
Shinoka 1996 (–)	Prospective animal study	17 piglets	Hct and deep hypothermic circulatory arrest	Higher Hct improves cerebral outcome
Habib 2003 (–)	Retrospective trial	5000	Effects of nadir Hct in CPB patients	Increased hemodilution was associated with worse organ dysfunction/morbidity
Swaminathan 2003 (–)	Prospective trial	1404	Association of Hct and acute renal injury	CPB hemodilution to Hct < 24% is associated with increased likelihood of renal injury (including ARF) and worse outcome
Habib 2005 (–)	Retrospective trial	1760	Hemodilutional anemia, transfusion and renal injury	CPB hemodilution to Hct < 24% is associated with increased likelihood of renal injury (including ARF) and worse outcome

*The studies' results are presented as positive results (+), negative results (–), or unclear results (±). CPB indicates cardiopulmonary bypass; Hct, hematocrit; RBC, red blood cell; Hb, hemoglobin; EO, emergent operation; LVEF, left ventricular ejection fraction; EF, ejection fraction.

Table 2. Prime Volume Reduction, Hyperoncotic Cardiopulmonary Bypass Prime and Retrograde Autologous Priming of the Cardiopulmonary Bypass Circuit for Reduction of Blood Product Transfusions*

Resource	Design	Number of Patients	Aim of the Study	Study Conclusion
Ferraris 2007 (+)	Review/guidelines	—	Guidelines for blood products conservation	MCs, RAP = class IIb (level of evidence B)
Wiesenack 2004 (+)	Partly retrospective and partly prospective study	970	MCs compared to CCPB circuits	Significantly lower transfusion rates with minimized circuits
Boettcher 2005 (+)	Case series	3	Small-volume CPB circuit	No blood or blood component transfusions
Fromes 2002 (+)	Prospective RCT	60	MC versus CCPB circuit	Reduced inflammatory response, hematocrit drop, platelet drop with MECC system
Abdel-Rahman 2005 (−)	Prospective RCT	204	MC versus CCPB circuit	Reduced inflammatory reaction with MECC system but not blood loss
Abdel-Rahman 2006 (−)	Prospective RCT	81	MC versus CCPB circuit	MC: blood loss not reduced but suppression of activation of coagulation and fibrinolytic cascades
Nollert 2005 (−)	Prospective RCT	30	MC versus CCPB circuit	Inflammation and coagulation variables affected marginally, decreased safety margins for volume loss, air emboli, and weaning
Sade 1985 (−)	Prospective RCT	83	Clinical effects of colloid versus crystalloid priming fluid	Blood product transfusions, platelet count, and blood viscosity had no clinical differences among groups
Lindberg 1985 (−)	Prospective trial	20	Dextran versus human plasma for priming solution	Dextran could replace human plasma for prime. No adverse events
Eising 2001 (−)	Prospective RCT	20	Colloid prime with HES 10% versus crystalloid prime (Ringer's lactate)	HES prime improves CI and prevents EVLW accumulation. No differences between groups in hematocrit values and in blood loss
Jansen 1996 (−)	Prospective RCT	20	Crystalloid versus colloid priming	Colloid priming = less adverse events, reduced hospital stay, but not reduced blood product transfusions
Rosengart 1998 (+)	Prospective RCT	60	Patients randomized to CPB with or without RAP	RAP decreases hemodilution and RBC transfusions
Shapira 1998 (+)	Prospective RCT	114	Full versus reduced (with RAP) prime volume	RAP reduces prime-induced hemodilution and blood products transfusions
Balachandran 2007	Prospective RCT	104	RAP versus conventional strategy	Reduced blood transfusions with RAP
Murphy 2004 (−)	Retrospective study	565	Impact of RAP in blood product reduction	Not statistically significant differences between the two groups in blood transfusions
Rousou 1999 (+)	Prospective study	175	Effectiveness of RAP in blood conservation	RAP = very effective, part of blood conservation strategies
Jansen 1995 (+)	Prospective study	40	Large (2350 mL) versus small (1400 mL) prime volume	Small prime volumes attenuate the hemodynamic response and reduce blood product requirements
Parrot 1991 (+)	Prospective RCT	66	Effectiveness of IBRS and MBRS	Significant blood transfusion reduction
Dalyrymple-Hay 2001 (+)	Prospective RCT	166	Efficacy of autotransfusion	Reduced allogeneic blood transfusion frequency

*The studies' results are presented as positive results (+), negative results (−), or unclear results (±). MCs indicates minimized circuits; RAP, retrograde autologous priming; CCPB, conventional cardiopulmonary bypass; CPB, cardiopulmonary bypass; RCT, randomized control trial; MECC, minimal extracorporeal circulation system; HES, hydroxyethyl starch; CI, cardiac index; EVLW, extravascular lung water; RBC, red blood cell; IBRS, intraoperative blood recovery system; MBRS, mediastinal drainage blood recovery system.

Table 3. Red Cell Saving Plasma Concentration Filters, and Parental Fluid Restriction for Reduction of Blood Product Transfusions*

Resource	Design	Number of Patients	Aim of the Study	Study Conclusion
Goodnough 2003 (+)	Review	—	Alternatives to blood transfusion	Routine use of autologous blood cell salvage
ASA Guidelines 2006	Practice guidelines for perioperative blood transfusions	—	Blood conservation strategies	Cell savage = routinely used in cardiac operations
Ferraris 2007 (+)	Review, guidelines	—	Blood conservation in cardiac operations	Routine use red cell saving (class A, level of evidence A)
Moran 1978 (+)	Prospective controlled study	96	Centrifugation of oxygenator contents after CPB	Safety and routine use
Cordell 1981 (+)	Prospective comparative study	214	Blood salvage before, during, and after cardiac operation	Very effective technique for reduction of blood product transfusions
Winton 1982 (+)	Clinical trial	20	Cell saver use in cardiac surgery	Save 105 ± 88.7 mL of packed red cells
Keeling 1983 (+)	Feasible study	725	Cardiovascular patients (75%), orthopedic procedures, splenectomy, craniotomy, ectopic pregnancies, caesarian sections, and exploratory laparotomy	Autotransfusion proved safe, efficient while conserving blood bank resources
Mayer 1985 (+)	Prospective RCT	20	One-third of the total intra- and postoperative transfusion needs using cell separator	Cell separator = valuable aid in autotransfusion technique
Hall 1990 (+)	Retrospective study	155	Cell saver apparatus: post-surgical bleeding and cost effectiveness	Reduced homologous blood transfusions but added to the cost of the procedure
Lee 1997 (+)	Retrospective study	162	Usefulness of autologous blood salvage	Decreased utilization of homologous blood
Tempe 2001 (+)	Comparative, prospective RCT	60	Cell saver versus aprotinin versus controls (3 groups of patients)	Cell saver is effective and comparable to aprotinin for blood conservations
Tempe 1996 (+)	Prospective RCT	150	Autologous blood and cell saver and oxygenator versus autologous blood only versus controls (3 groups of patients)	Cell saver helps in blood product reduction especially in small-size patients
Murphy 2004 (+)	Prospective RCT	200	Intra- and postoperative cell saver versus homologous blood transfusions only (2 groups of patients)	Cell saver = safe and effective method for the reduction of blood transfusions
Svenmarker 2003 (+)	Prospective RCT	33	Cardiotomy suction versus cell saver salvage in CPB with reference to inflammatory response	Cell saver reduces hemolysis and may lower the dose of the inflammatory components
Despotis 1996 (–)	Comparative study	487	Factors associated with excessive postoperative blood loss	Cell saver extensive use may lead to a bleeding diathesis
Merville 1991 (±)	Prospective RCT	120	Effectiveness of cell saver	Unclear results
Dietrich 1989 (+)	Prospective RCT	100	Effectiveness of blood conservations techniques	Considerably reduced blood requirements. Cell saver very effective among other techniques
Daane 2003 (±)	Prospective RCT	40	Effectiveness of processing CPB volume in blood transfusions	Processing CPB volume may result in reducing the volume of transfusion needed of allogeneic blood products
Gray 2001 (+)	Comparative, prospective study	62	Effectiveness of cell salvage with autotransfusion using leukocyte reduction filters	Low homologous transfusion rates and autologous predonation. Not early biochemical progression in malignancies.
Boonstra 1985 (+)	Prospective study	28 + 80	Effectiveness of controlled cardiotomy suction during clinical membrane oxygenator perfusions	Reduced platelet activation and improved hemostatis

Thurer 1979	Prospective RCT	113	Safety and effectiveness of autotransfusion	No difference in allogeneic blood transfusion
Boodhwani 2010 (−)	Prospective RCT	65	Assess the feasibility of testing modified ultrafiltration as a blood conservation technology in cardiac surgery	Not statistical significance in RBC transfusions, more frequent vasopressor use
Babka 1997 (±)	Prospective RCT	60	Effectiveness of the ultrafiltration technique in reducing hemodilution	No improvement in the quality of care
Raman 2003 (±)	Prospective comparative study	118	Effectiveness of hemofiltration in CPB	Perhaps reduced postoperative bleeding and pulmonary complications
Grunenfelder 2010 (−)	Prospective RCT	97	Evaluation of the clinical impact of MUF	MUF led to a significant reduction in cytokine and adhesion molecule levels. No significant impact in outcome
Vretzakis 2005 (+)	Prospective RCT	121	Evaluation of the influence of BIS monitoring on decision making during cardiac anesthesia	BIS provides better assess of the state of vital functions and reduction in RBC transfusions with a restrictive fluid protocol
Vretzakis 2010 (+)	Prospective RCT	192	Effectiveness of fluid restriction on reduction of RBC requirements	Fluid restriction is very effective in reducing RBC transfusions during surgery

*The studies' results are presented as positive results (+), negative results (−), or unclear results (±). CPB indicates cardiopulmonary bypass; RCT, randomized clinical trial; RBC, red blood cell; MUF, modified ultrafiltration; BIS, bispectral index.

2003; Habib 2005] suggest that marked hemodilution can have adverse consequences, including renal dysfunction and worsened clinical outcome. Because data on safety of low hematocrit values during CPB are conflicting, there is clearly room for subjectivity in the decision to transfuse, especially in women and men with low body surface area, where hemodilution is more pronounced [DeFoe 2001]. Under hemodilution, clinicians should attempt to estimate the degree of anemia that the patient can safely tolerate by considering variables other than Hb or hematocrit values; lack of such measurements leads to adoption of "transfusion triggers" and may explain the increased blood product usage in easily hemodiluted patients. The above studies and their results are presented in Table 1.

Because volume load is modifiable, net fluid balance during operations under CPB can be reduced by interventions such as prime volume minimization with or without use of hyperoncotic solutions, retrograde autologous CPB circuit priming, cell salvage techniques, and use of plasma concentration filters.

PRIME VOLUME REDUCTION

Low prime volume is of primary importance for hemodilution attenuation, and therefore numerous efforts have been made to minimize circuit volume. Conventional circuit volume can exceed 1400 mL for the pump and the oxygenator, but the volume needed is reduced to 450 mL in newer integrated circuits combining the centrifugal pump and the oxygenator. We examined 7 articles that focus on the effectiveness and safety of the minimized circuits (MCs) (Table 2) [Fromes 2002; Wiesenack 2004; Abdel-Rahman 2005; Boettcher 2005; Nollert 2005; Abdel-Rahman 2006; Ferraris 2007]. Most of them are prospective randomized control trials (RCTs) [Fromes 2002; Abdel-Rahman 2005; Nollert 2005; Abdel-Rahman 2006], and most of these RCTs show no special benefit when MCs are compared to conventional CPB circuits [Abdel-Rahman 2005; Nollert 2005; Abdel-Rahman 2006]. A partly retrospective and partly prospective study of 970 elective CABG patients including valve replacement operations showed significantly lower transfusion rates with MCs compared to conventional circuits [Wiesenack 2004].

Cardiac surgery is particularly challenging in Jehovah's Witness patients, especially children, because these patients reject not only homologous transfusion, but also re-transfusion of autologous blood temporarily separated from their own circulation. In one report, open-heart surgery was successfully performed in 3 Jehovah's Witness infants (body weight between 3.1 and 4.5 kg) without any blood component transfusion using a small-volume CPB circuit with a 200-mL priming volume [Boettcher 2005].

Generally, CPB and CPB circuits trigger a significant systemic inflammatory response through complement activation and pro-inflammatory cytokine release [Laffey 2002]. Interestingly, data suggest that use of MCs reduces inflammatory reaction, activation of coagulation, and fibrinolysis and that their beneficial effects on inflammation and hemodilution may reduce the need for allogeneic blood transfusions [Fromes 2002], although studies did not show reduced blood products transfusions [Abdel-Rahman 2005; Abdel-Rahman 2006]. A RCT of 204 CABG patients found no change in transfusion requirements with use of a MC [Nollert 2005], and the authors of this study concluded that, when considering MCs, any potential transfusion benefits from their use must be weighed against possible risks including air embolism. Several MCs are currently commercially available, and their use is rapidly increasing as more and more anesthesiologists, perfusionists, and surgeons are trained and become aware of their advantages.

The use of low prime and minimized extracorporeal bypass circuits in order to reduce hemodilution during CPB is classified in the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists report in Class IIb (level of evidence B) as not unreasonable for blood conservation [Ferraris 2007]. The true impact of MCs on transfusion inflammatory response and outcome, however, are largely unknown and deserve further investigation. The articles that focus on the effectiveness and safety of MCs are presented in Table 2.

HYPERONCOTIC CARDIOPULMONARY BYPASS PRIME

Marked colloid osmotic pressure (COP) reduction due to hemodilution upon CPB initiation may be a significant factor adversely affecting post-CPB organ function. Acute COP reduction causes an imbalance between microvascular net filtration and lymphatic interstitial fluid removal, thereby leading to edema formation. Extravascular lung water excess and myocardial edema can contribute to cardiopulmonary dysfunction [Boldt 1986; Goto 1991; Boldt 1999]. Presently, the optimal priming fluid composition for the CPB circuit is unknown, and the impact of priming fluid composition on post-CPB organ dysfunction remains controversial. In Table 2, 4 prospective RCTs that compare different priming fluids are presented [Lindberg 1985; Sade 1985; Jansen 1996; Eising 2001]. Three of these studies evaluating colloid as priming fluid failed to show any clinical benefit or outcome improvement [Lindberg 1985; Sade 1985; Eising 2001], perhaps because (1) COP of these hyperoncotic priming solutions was still less than physiologic, and (2) crystalloid cardioplegia was used. Currently, because many centers use blood cardioplegic solution drained from the reservoir, COP reduction may be avoided with hyperoncotic priming. A RCT of 20 patients undergoing elective coronary artery surgery using heparin-coated circuits and crystalloid cardioplegia showed improved clinical performance and shorter postoperative hospital stay in the colloid CPB prime group, but did not show reduced blood product transfusions [Jansen 1996].

In a later study comparing hydroxyethyl starch (HES) versus crystalloid, COP reduction and net fluid balance were significantly reduced and hemodynamic parameters and functional respiratory variables such as $AaDO_2$ and Qs/Qt were improved in the HES group [Lindberg 1985]. Hb and hematocrit values 2 and 4 hours after surgery did not differ between groups, however, and despite a trend toward increased blood loss in the HES group, outcome did not differ between groups. At present, use of hyperoncotic priming solutions and attenuation of COP reduction do not have any documented impact on blood product use in cardiac surgery, but studies addressing this important issue are currently underway (www.clinicaltrials.gov NCT00182377).

RETROGRADE AUTOLOGOUS PRIMING OF THE CARDIOPULMONARY BYPASS CIRCUIT

Retrograde autologous priming (RAP) of the CPB circuit was first described in 1960 [Panico 1960] and revived in the late 1990s [Rosengart 1998] in an attempt to limit hemodilution on CPB initiation. RAP involves replacement of the crystalloid prime by the patient's own blood. After arterial and venous cannulae are in place, up to 1 L of crystalloid prime is slowly drained into a recirculation bag and replaced by the patient's blood immediately before CPB initiation [Rosengart 1998]. A 1000-mL blood transfer bag is connected to the venous line, and RAP is performed in 3 basic steps. First, crystalloid is displaced from the arterial line into the blood transfer bag by blood allowed to flow backwards from the aorta into the arterial line and filter. Next, crystalloid in the venous reservoir and oxygenator is displaced by blood flowing backwards from the aorta. Finally, the remaining prime is displaced from the venous line into the bag on CPB initiation. Approximately 300 mL of CPB circuit prime volume is replaced in each step, and the entire RAP process can be completed in 5 to 8 minutes. This technique maintains COP and reduces extravascular lung water compared with standard priming techniques.

However, hypovolemia, as blood is drained from the patient into the arterial and venous lines, can result in hemodynamic instability. Hypotension can be treated with phenylephrine (bolus or infusion) and/or crystalloid administration during the (usually brief) period before the pump reaches acceptable flow for organ perfusion, but crystalloid administration at this stage mitigates the RAP effect. If hemodynamic instability persists despite these measures, the RAP process must be terminated. Because RAP generally causes hypovolemia in the patient-circuit system, the perfusionist must be trained in its use and remain vigilant in order to preserve organ perfusion.

Eight studies examine the effectiveness and safety of RAP (Table 2) [Parrot 1991; Jansen 1995; Rosengart 1998; Shapira 1998; Rousou 1999; Dalrymple-Hay 2001; Balachandran 2002; Murphy 2004]. The efficacy of RAP in reducing the number of patients transfused and/or total blood product use has been demonstrated in almost all of these studies [Jansen 1993; Jansen 1995; Rosengart 1998; Shapira 1998; Rousou 1999; Dalrymple-Hay 2001; Balachandran 2002]. A retrospective study, however, showed minimal, nonsignificant reduction in packed red cell (PRC) use with routine RAP [Murphy 2004], with 44% of patients in the RAP group receiving PRCs versus 51% in the control group. Patients with larger initial red cell mass derived a greater benefit from RAP, but interpretation of these results is limited by retrospective study design. In a later analysis, the same investigators found decreased incidence of postoperative cardiac arrest in the RAP group and no change in other adverse events, thus suggesting that RAP is a safe technique [Murphy 2006]. The observed reduction in blood product transfusions makes the technique part of the blood conservation strategies [Rousou 1999]. Other investigators observed no effect of RAP on postoperative or total transfusion requirements and concluded that RAP, by reducing crystalloid fluid administration and COP reduction during CPB, reduces post-CPB weight gain [Eising 2003]; however, these trials excluded patients at high risk for transfusion and were limited by small RAP group size.

A database study attempted to determine the effect of different prime volumes on postoperative hyperdynamic response by comparing patients with large CPB prime (2350 mL) versus patients with small (1400 mL) CPB prime volume [Jansen 1995]. COP was higher, fluid balance was less positive, and the hyperdynamic response was partly attenuated in the small prime volume group, and the authors concluded that using small prime volumes can reduce blood product use. In 2 other RCTs, use of RAP significantly reduced allogeneic blood transfusion frequency [Jansen 1991; Dalrymple-Hay 2001]. Studies investigating the impact of small volume CPB circuits in combination with retrograde autologous CPB circuit priming are currently underway (www.clinicaltrials.gov NCT00646373). Based on current evidence, retrograde autologous CPB circuit priming is classified as "not unreasonable" (Class IIb, level of evidence B) for blood conservation in the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists practice guidelines [Ferraris 2007].

RED CELL SAVING

Autologous blood cell salvage is used routinely in many parts of the world in cardiac [ASA Task Force on Perioperative Blood Transfusion and Adjuvant Therapies 2006] and other high-risk operations [Goodnough 2003]. We studied 3 reviews [Goodnough 2003; ASA Task Force on Perioperative Blood Transfusion and Adjuvant Therapies 2006; Ferraris 2007] and 17 clinical trials [Moran 1978; Thurer 1979; Cordell 1981; Winton 1982; Keeling 1983; Mayer 1985; Dietrich 1989; Hall 1990; Merville 1991; Despotis 1996; Tempe 1996; Lee 1997; Gray 2001; Tempe 2001; Daane 2003; Svenmarker 2003; Murphy 2004] (Table 3). Most of the trials are RCTs [Moran 1978; Thurer 1979; Mayer 1985; Dietrich 1989; Merville 1991; Tempe 1996; Tempe 2001; Daane 2003; Svenmarker 2003; Murphy 2004]. Overall, 16 studies and reviews show positive results. Intraoperative autotransfusion with a cell saver involves recovery of the patient's own blood from the surgical wound, washing and/or filtering, and re-infusion into the circulation. According to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists guidelines, routine use of red cell saving is helpful for blood conservation in cardiac operations using CPB, except in cases of infection or malignancy (Class A, level of evidence A) [Ferraris 2007]. Today, cell saving devices can process quickly even small amounts of blood, require small priming volumes, continuously return high quality blood during and after surgery, and can collect blood not only during heparinization, but also when there is no heparin effect (eg, during internal mammary artery preparation). Several reports document the safety of the cell saver and support its routine use in cardiac surgery as a means to reduce blood transfusion [Moran 1978; Cordell 1981; Winton 1982; Keeling 1983; Mayer 1985; Hall 1990; Lee 1997; Tempe 2001], and intraoperative autologous blood donation combined with cell saver use decreases transfusion requirements in small-size patients (mean body weight of 45 kg) [Tempe 1996]. In a recent RCT, patients scheduled for CABG were randomized to autotransfusion (receiving autotransfused washed blood from intraoperative cell salvage and postoperative mediastinal fluid cell salvage, n = 98), or control (receiving stored homologous blood only, n = 102). Postoperative blood loss, fluid requirements, and adverse events did not differ between groups, but patients in the autotransfusion group were significantly less likely to receive homologous blood transfusions and received significantly fewer units of blood. Autotransfusion did not produce any significant derangement on thromboelastograph or laboratory coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen, and fibrinogen D-dimer levels) [Murphy 2004]. Concern has been raised regarding transfusion of cytokines through autologous shed blood [Arnestad 1994], but this concern is diminished because modern salvage is associated with reduced circulating markers of systemic inflammation [Perttila 1995; Amand 2002; Jewell 2003; Svenmarker 2003].

After weaning from CPB, perfusionists drain the CPB circuit to the saving apparatus in order to limit red cell wasting. Salvage of CPB circuit blood is a reasonable attempt at blood conservation (level of evidence C) [Tinmouth 2005] and is routinely performed in many centers. In one RCT, residual pump blood processed with an autotransfusion system was better than unprocessed blood in terms of complement activation, coagulation factors, and stimulation of interleukin-6 (IL-6) and IL-8 [Walpoth 1999]. The better postoperative clinical course in the processed blood group patients was attributed to reduced load of retransfused activated mediators; however, extensive use of cell salvage systems to process the extracorporeal circuit content after CPB discontinuation may lead to coagulation factor and platelets loss, resulting in a bleeding diathesis [Despotis 1996]. Existing studies cannot provide conclusive answers, so the impact of CPB circuit blood salvage on allogeneic blood transfusion requirements remains unclear [Dietrich 1989; Merville 1991; Daane 2003]. It is noteworthy that, according to recent data, savers used in combination with leukocyte depletion filters or salvaged blood irradiation may be of benefit in oncologic surgery [Hansen 1999; Thomas 1999; Gray 2001], and therefore the dogma that salvage is contraindicated in malignancy is now questioned.

Aspiration of mediastinal blood from the operative field with the cardiotomy suction, followed by direct reinfusion is performed routinely and can occasionally be life-saving ("sucker bypass"). However, "uncontrolled" cardiotomy suction during prolonged CPB (>3 hours) may be associated with increased postoperative bleeding [Boonstra 1985]. Cardiotomy suction in combination with a cell saving apparatus is routinely practiced worldwide. In most cases, blood from the field is processed by the saver when there is no heparin, whereas during heparinization cardiotomy blood is directly reinfused. Direct reinfusion of mediastinal blood drained postoperatively from the chest tube is not recommended and may cause harm (Level of evidence B) [Ferraris 2007]. In cases of extensive postoperative bleeding, collected blood must be processed by a saver before reinfusion. In conclusion, because approximately half of the blood suctioned from the patient is ultimately reconstituted with usual red blood cell conservation protocols, appropriate cell saver use during and after cardiac surgery may reduce overall transfusion requirements.

PLASMA CONCENTRATION FILTERS

Filters are often used in cardiac surgery to remove excess fluid administered on CPB initiation. Hemoconcentration is based on transmembrane pressure-driven ultrafiltration and involves the separation of plasma fluid and low molecular solute substances from diluted blood with a membrane filtering blood components and proteins. There are no absolute contraindications to hemoconcentration, but infection, hemolysis, and embolism are potential complications. To avoid hemolysis, filters should be primed before running, with priming volume ranging, depending on device type, between 15 and 100 mL. Of note, addition of crystalloid to the CPB circuit is often required in order to maintain adequate circulating volume during hemofiltration, but may counteract the favorable hemofiltration effect on hemodilution. The net effect of hemofiltration on total body water reduction and transfusion needs is unclear: We present 4 studies [Babka 1997; Grunenfelder 2000; Raman 2003; Boodhwani 2010] with negative or unclear results (Table 3). A RCT of 60 patients assigned to hemofiltration versus standard CPB did not show any allogeneic blood product use reduction, and the researchers concluded that routine ultrafiltration during coronary artery bypass surgery with CPB does not improve quality of care [Babka 1997]. Another retrospective study comparing 61 patients treated with hemofiltration versus 57 patients treated with CPB alone showed a trend toward decreased bleeding during high-risk cardiac surgery in the hemofiltration group [Raman 2003], with this beneficial hemofiltration effect possibly related to inflammatory mediator removal and improved hemodynamic indices. The hemofiltration effect on inflammatory response seems more prominent with modified filters. A RCT of 97 patients compared a modified filter to conventional CPB and showed no difference in blood loss between groups, but adhesion molecules and cytokines were significantly reduced in the filter group [Grunenfelder 2000].

A very recent multicenter RCT with 65 patients assessed the feasibility of a modified ultrafiltration in patients with CPB versus circulation without an interposed filter. Differences in RBC transfusions between groups did not reach statistical significance, but introduction or increase in dose of vasopressors was more frequent in the modified ultrafiltration group [Boodhwani 2010].

Because the impact of hemofiltration on transfusions is currently unclear, routine ultrafiltration during or immediately after CPB is considered not helpful for blood conservation in adult cardiac operations (Class III, level of evidence B) [Ferraris 2007]. Nevertheless, experienced perfusionists use hemofiltration in selected cases in an attempt to reverse excessive hemodilution and improve fluid balance, especially when response to diuretics is not satisfactory and/or a cell saver is not available.

PARENTERAL FLUID RESTRICTION

Because hemodilution is a major factor influencing the decision to transfuse in clinical practice, limiting hemodilution may reduce transfusions in cardiac operations involving CPB. Prime volume reduction, MC, RAP, hemofiltration, and diuretics may be beneficial in these operations mainly because they reduce extracellular volume expansion. Many practitioners attempt to limit positive fluid balance by avoiding excessive parenteral fluid administration. Surprisingly, data on the effect of intraoperative fluid restriction on transfusion needs are very limited. Recently, a RCT involving 130 patients undergoing CABG under CPB reported significant reduction of intraoperative PRC transfusions with a restrictive parenteral fluid protocol, aided by near infra-red spectrophotoscopy (INVOS) [Vretzakis 2005], and a more recent randomized trial evaluating the impact of fluid restriction on blood transfusions demonstrated significant reduction of intraoperative packed red cell transfusions in cardiac surgery patients treated with a fluid restriction protocol. Transfusions in the intensive care unit (ICU) were not significantly different, and discharge hematocrit did not differ significantly between the restrictive and the liberal fluid administration groups (Table 3) [Vretzakis 2010].

The role of newer monitoring technologies on decision-making during cardiac surgery deserves careful evaluation because every piece of information may help better assess the state of vital functions. In a prospective randomized trial, information from the bispectral index (BIS) monitor prompted intervention on a number of occasions during mild hypothermic CPB, but only 70% of these interventions targeted hypnotic state depth, whereas 30% of them addressed other aspects of patient care [Vretzakis 2005].

Most intraoperative transfusions occur during CPB, when SVO_2 monitoring with a pulmonary artery catheter is not feasible, and venous Hb saturation on venous cannula blood samples gives an inconclusive picture of tissue oxygenation because the heart is bypassed. In this setting, transfusion decisions are usually based on Hb values, using a predetermined "transfusion trigger." In reality, however, nobody knows what is best for a patient with low hematocrit (15% or less) during CPB. Is a blood transfusion needed/justified when hematocrit is low, but brain tissue oxygen saturation, measured by INVOS, remains normal? Because the answer to this important question is unknown, we all hope that newer monitoring modalities will help decision-making by providing meaningful physiologic data. The impact of INVOS monitoring on allogeneic transfusions in cardiac surgery is currently under investigation (www.clinicaltrials.gov 00879463).

CONCLUSION

At the present time, several blood conservation interventions have been proposed during cardiac surgery, and a multimodal approach to blood conservation may be beneficial, particularly in high-risk patients. The anesthesiologist has a significant role during cardiac surgery; he can facilitate blood conservation efforts by limiting dilutional anemia through limitation of positive fluid balance before or/and during CPB, but doing so requires coordination with the perfusionist and the cardiac surgeon.

Current evidence suggests that there is significant room for improvement in physician transfusion practices during cardiac surgery. Appropriately designed rigorous clinical trials are needed to determine the effectiveness of intraoperative interventions on blood conservation and the role of new monitoring modalities in rational decision-making regarding blood product use in cardiac surgery.

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