Review Article

Blood Conservation—A Team Sport

Donald S. Likosky, PhD,* Timothy A. Dickinson, MS;† Theron A. Paugh, CCP*

*Section of Health Services Research and Quality, Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan; and †Specialty Care, Nashville, Tennessee for the Michigan Society of Thoracic and Cardiovascular Surgeons and the Perfusion Measures and Outcomes (PERForm) Registry

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Abstract: Cardiac surgery accounts for between 15% and 20% of all blood product utilization in the United States. A body of literature suggests that patients who are exposed to even small quantities of blood have an increased risk of morbidity and mortality, even after adjusting for pre-operative risk. Despite this body of literature supporting a restrictive blood management strategy, wide variability in transfusion rates exist across institutions. Recent blood management guidelines have shed light on a number of potentially promising blood management strategies, including acute normovolemic hemodilution (ANH) and retrograde autologous priming (RAP). We evaluated the literature concerning ANH and RAP, and the use of both techniques among centers participating in the Perfusion Measures and outcomes (PERForm) registry. We leveraged data concerning ANH and RAP among 10,203 patients undergoing isolated coronary artery bypass grafting (CABG) procedures from 2010 to 2014 at 27 medical centers. Meta-analyses have focused on the topic of ANH, with few studies focusing specifically on cardiac surgery. Two meta-analyses have been conducted to date on RAP, with many reporting higher intra-operative hematocrits and reduced transfusions. The rate of red blood cell transfusions in the setting of CABG surgery is 34.2%, although varied across institutions from 16.8% to 57.6%. Overall use of ANH was 11.6%, although the utilization varied from 0.0% to 75.7% across institutions. RAP use was 71.4%, although varied from 0.0% to 99.0% across institutions. A number of blood conservation strategies have been proposed, with varying levels of evidence from meta-analyses. This uncertainty has likely contributed to center-level differences in the utilization of these practices as evidenced by our multi-institutional database. Perfusion databases, including the PERForm registry, serve as a vehicle for perfusionist’s to track their practice, and contribute to multidisciplinary team efforts aimed at assessing and improving the value of cardiac surgical care. Keywords: blood transfusion, blood conservation, cardiopulmonary bypass, surgery.

Cardiac surgery is a large consumer of blood, accounting for between 15% and 20% of all blood product utilization in the United States (1). Indeed, nearly 50% of patients undergoing coronary artery bypass grafting (CABG) surgery are exposed to red blood cell (RBC) products. Although some literature exists to support a lack of superiority of a restrictive transfusion threshold (2), a body of work has documented worse outcomes associated with even low volume (e.g., <3 units) transfusions, including a 16% increased odds of mortality and a 27% increased odds of morbidity (3,4). Although the mechanism underlying this observation is not completely understood, some have argued that value nonetheless remains in continued advocacy for blood conservation given the association between RBC utilization and morbidity, mortality and resource utilization (5).

While some RBC utilization may be given to address surgical bleeding, others may be given to address the hemodilutional effects associated with the use of extracorporeal circuits. Recent blood management guidelines have shed light on some potentially promising blood management strategies (6). Unfortunately, although some recommendations are well supported in the literature (e.g., mini-circuits, Class I, Level A), others lack robust...
evidence to support a given clinical strategy, including the use of acute normovolemic hemodilution (ANH) (Class IIb, Level B) and retrograde autologous priming (RAP) (Class IIb, Level B) (7). Efforts aimed at a more rational approach toward blood management would likely benefit from a broader understanding of the literature supporting these and other potentially effective blood conservation strategies.

In this article, we provide a critical appraisal of the literature supporting two perfusion-related blood management practices (ANH, RAP). We review the literature supporting these practices as well as emerging findings from the Perfusion Measures and Outcomes (PERForm) registry, a multi-institutional perfusion database (8).

### MATERIALS AND METHODS

#### 2011 Blood Management Guidelines

The Society of Thoracic Surgeons (STS), in conjunction with the Society of Cardiovascular Anesthesiologists (SCA), and the American Society of Extracorporeal Technology’s International Consortium for Evidence-Based Perfusion (ICEBP) published its most recent 2011 Blood Management Guidelines (6). The guidelines leveraged the American Heart Association and American College of Cardiology’s approach toward developing evidence-based guidelines. While the guideline document covers a broad-ranging set of practices, a number of them focus specifically on those that involve cardiovascular perfusionists (Table 1). In this manuscript, we focus specifically on the recommendations regarding ANH and RAP.

#### Introduction to the PERForm Registry

In this manuscript, we provide data concerning ANH and RAP use across institutions participating in the Perfusion Measures and Outcomes (PERForm) registry. We used data from 10,203 patients undergoing isolated CABG procedures from 2010 to 2014 at 27 medical centers.

The PERForm registry was established in 2010 as a voluntary database. Current efforts are focused on identifying perfusion practices associated with improved outcomes and providing benchmarking opportunities to support local and multi-institutional quality improvement initiatives. Although initial efforts focused on recruiting all 33 institutions participating in the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC), a growing number of institutions are located outside of Michigan.

The PERForm registry contains fields related to the care and conduct of cardiovascular perfusion practices (8). A description of our methodological approach toward collection and merging of surgical and perfusion records from each institution has previously been published (9). Participating institutions are routinely audited for data validity and accuracy as part of the MSTCVS-QC audit system.

### RESULTS

The rate of RBC transfusions in the setting of CABG surgery is 34.2%, although varies across institutions from 16.9% to 57.6% (Figure 1).

#### Acute Normovolemic Hemodilution

The STS/SCA/ICEBP Blood Management Guidelines provided the following recommendation concerning ANH use.

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**Table 1. Summary of meta-analyses concerning acute normovolemic hemodilution.**

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Articles (Patients)</th>
<th>Cohort</th>
<th>Cardiac-Specific Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryson (13)</td>
<td>24 trials (1,218)</td>
<td>Mixed</td>
<td>Transfusion (3 articles): OR = .51 (.26, .99)</td>
</tr>
<tr>
<td></td>
<td>Cardiac: 11 trials (381)</td>
<td></td>
<td>Difference in blood units (2 articles): −2.83 (−5.34, −.31)</td>
</tr>
<tr>
<td>Segal (11)</td>
<td>42 trials (2,233)</td>
<td>Mixed</td>
<td>Difference in blood loss (1 articles): −2.33 (−4.59, −5)</td>
</tr>
<tr>
<td>Curley (14)</td>
<td>22 trials (2,618)</td>
<td>Cardiac and vascular</td>
<td>None provided</td>
</tr>
<tr>
<td></td>
<td>Cardiac: 9 trials (856)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 1.** Center-level variation in total perioperative red blood cell units transfused. Each bar represents the percent use of 1 (light gray), 2 (medium gray), or ≥3 (black) units transfused at a given institution among isolated CABG procedures between 2010 and 2014. The x axis represents unique institutions contributing cases.
Acute normovolemic hemodilution may be considered for blood conservation but its usefulness is not well established. It could be used as part of a multiprongs approach to blood conservation. (Class IIb, Level of evidence B)

**Literature supporting ANH use:** Introduced in the 1970s, ANH entails removing blood volume from the patient prior to the onset of cardiopulmonary bypass (CPB), and maintaining adequate normovolemia using volume within the patient by replacing 1:1 with crystalloid and/or colloid replacement solutions. Although there are contraindications for ANH, such as anemia, bacteremia, sepsis and low ejection fraction, other risks are mitigated by re-infusing this blood volume as necessary (10). Theoretically, ANH benefits the patient by reducing exposure to allogeneic blood products and any risk therein associated with such transfusions (e.g., viral pathogens) (11). ANH preserves RBC mass, platelets, and other important components of whole blood by reducing the concentration of these elements in obligatory shed blood during the procedure. In addition, sequestering the patient’s whole blood prevents any CPB-related insults (e.g., platelet activation, initiation of the inflammatory cascade) (10,11). A number of theoretical side effects associated with the ANH procedure, while potentially rare, include 1) dilutional anemia, possibly leading to end organ ischemia and 2) hypotension induced from hypovolemia (12). These adverse sequelae have been inconsistently reported in the literature.

Although the most recent recommendation for ANH is IIb (B), meta-analyses also inform the evidence-base supporting this practice (Table 1). The earliest meta-analysis was by Bryson et al. which included 24 trials, including 1,218 patients undergoing cardiac, gastrointestinal, thoracic, hepatic, ear-nose-throat, urological, or vascular procedures (13). The authors conducted a broad search of articles from 1966 to 1996, and limited articles to those comparing intra-operative ANH with a current (as of that time period) control group. While a mix of procedures was included in the project, topic-specific analyses were conducted related to transfusion exposure, blood volume transfused, and peri-operative blood loss. ANH significantly reduced the odds of transfusion (odds ratio [OR] = .51, .26–.99). Significant heterogeneity existed in the other outcomes measures. Segal et al. conducted a meta-analysis of articles spanning from 1966 to 2002 (11). Two independent investigators reviewed the articles. Articles were excluded if they did not have a control group; involved animals or in vitro studies, only included an abstract or were published in a language other than English. In total, 42 articles were included in their analysis, spanning the time period of 1972–2002. The analysis encompassed a variety of procedures, including but not limited to cardiac surgery, hip arthroplasty, radical prostatectomy, and spinal surgery. ANH use was equally effective at reducing allogeneic transfusions compared to usual care (relative risk [RR] = .96, .90–1.01) or other blood conservation methods (RR = 1.11, .96–1.28).

Although 18 of the 42 studies comprising this meta-analysis were from cardiac surgery, cardiac surgery-specific estimates were not provided. Interestingly, patients who were hemodiluted received fewer transfusions, had less total bleeding, although more intra-operative bleeding. Curley et al. (14) conducted a meta-analysis of articles up through 2013. Although not specifically focused on studying the efficacy of ANH per se, the investigators included articles in which patients were randomized to different transfusion thresholds in the setting of cardiac and/or vascular surgery. Of the trials included in this paper, ANH did not significantly impact the rate of transfusions (RR = .83, .35–1.95).

In conclusion, current findings from the meta-analyses and evidence-based guidelines suggest that ANH may be beneficial in reducing transfusions, although further evidence is warranted.

**Use of ANH across institutions participating in PERForm:** Overall use of ANH in the setting of CABG surgery is 11.6%, although the utilization varies from .0% to 75.7% across institutions, Figure 2.

**Retrograde Autologous Priming**
The STS/SCA/ICEBP Blood Management Guidelines provided the following recommendation concerning RAP use.

**RAP of the CPB circuit may be considered for blood conservation. (Class IIb, Level of evidence B)**

![Figure 2. Center-level variation in the use of ANH. Each bar represents the percent of ANH use at a given institution among isolated CABG procedures between 2010 and 2014. The x axis represents unique institutions contributing cases.](J Extra Corpor Technol. 2016;48:99–104)
A number of theoretical side effects associated with the RAP approach include 1) hypotension secondary to hypovolemia, 2) hypovolemia leading to lower reservoir volumes during CPB and insufficient de-airing of venous returned blood, and 3) higher hematocrit (Hct) levels (from less hemodilution) during CPB might increase RBC hemolysis (15).

**Literature supporting RAP use:** Rosengart et al. in a pilot study of 60 patients undergoing first-time CABG surgery, introduced the concept of replacing the crystalloid asanguineous component prime of the extracorporeal circuit with the patient’s own blood (16). By doing so, the investigators hypothesized that they could reduce hemodilution, and potentially the need for blood product transfusions. In this series, patients exposed to RAP had lower nadir Hct (20% vs. 22%, \( p = .002 \)), fewer intra-operative transfusions (3% vs. 23%, \( p = .03 \)), and fewer homologous RBC transfusions during the hospitalization (27% vs. 53%, \( p = .03 \)).

Two meta-analyses have been conducted to date on the topic of RAP (15,17). The most recent meta-analysis was authored by Sun et al. (15) which focused on the efficacy of RAP in reducing transfusions and post-operative outcomes among adult patients undergoing cardiac surgery (15). Although not excluding articles based on language or publication date, Sun reported on 10 trials (1,123 patients) published from 1998 to 2010. Findings from the articles comprising Sun’s meta-analysis are summarized in Table 2. Two of these articles are written in Chinese (Yang J, et al. Chin J ECC 2010; Zhao Y, et al. Chin J ECC 2010), and are not included in this report. Interestingly, one of the articles (18) did not appear to be a randomized clinical trial (RCT) but rather two consecutive series of patients undergoing isolated CABG surgery. Overall, many (although not all) of the studies (19) reported higher intra-operative Hcts (16,18,20) and reductions in transfusion requirements (16,18,20–23).

Studies to date have documented varying effectiveness of RAP in reducing transfusion rates, and have to our knowledge reported equivalent (or improved) outcomes associated with RAP use (16,18–24).

**Use of RAP across institutions participating in PERForm:** Use of RAP in the setting of CABG surgery is 71.4%, although varies from .0% to 99.0% across institutions (Figure 3). Additional studies are warranted to improve

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Patients</th>
<th>Cohort</th>
<th>Design</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosengart (1998) (16)</td>
<td>60</td>
<td>First-time CABG (pilot study)</td>
<td>RCT</td>
<td>Nadir Hct on CPB was higher among patients receiving RAP; RBC units/patient did not differ, but patients receiving RAP were less likely to be transfused intra-operatively and during their overall length of stay</td>
</tr>
<tr>
<td>Shapira (1998) (20)</td>
<td>114</td>
<td>Mixed</td>
<td>RCT</td>
<td>Nadir Hct on CPB was higher among patients receiving RAP; similar morbidity and mortality; total units/patient and percent transfused/pt was less among patients receiving RAP</td>
</tr>
<tr>
<td>Rousou (1999) (18)</td>
<td>175</td>
<td>Non-emergent isolated CABG excluded: those with preoperative coagulopathy, and elevated creatinine</td>
<td>Non-randomized</td>
<td>Patients receiving RAP had higher intra-operative Hct and reduced need for transfusions (among those with pre-CPB Hct ≤ 35% and those with BSA ≤ 2 m²).</td>
</tr>
<tr>
<td>Balachandran (2002) (21)</td>
<td>100</td>
<td>Isolated CABG</td>
<td>RCT</td>
<td>Patients receiving RAP had higher Hct in the ICU and hospital discharge and reduced need for and volume of blood transfused</td>
</tr>
<tr>
<td>Eising (2003) (24)</td>
<td>20</td>
<td>Elective CABG (pilot study)</td>
<td>RCT</td>
<td>Patients receiving RAP had lower extravascular lung water and weight gain. Transfusion was not reported.</td>
</tr>
<tr>
<td>Sobieski (2005) (23)</td>
<td>222</td>
<td>Mixed</td>
<td>RCT</td>
<td>No difference in total crystalloid volume; patients receiving RAP had 622 mL reduced prime volume, reduced use for hemoconcentrators, and reduced transfusion requirements.</td>
</tr>
<tr>
<td>Hou (2009) (22)</td>
<td>120</td>
<td>Elective, primary patients with BSA &lt;1.5 m² undergoing mixed cardiac procedures</td>
<td>RCT</td>
<td>Patients receiving RAP had reduced transfusion requirements, and lower average number of transfusions (intra- and peri-operatively). Clinical outcomes were similar.</td>
</tr>
<tr>
<td>Reges (2011) (19)</td>
<td>62</td>
<td>CABG, excluded patients &lt;18 or &gt;85 years; LVEF &lt; 30% and emergency surgery</td>
<td>RCT</td>
<td>Patients receiving RAP had higher Hct during CPB while no statistically significant reduction in need for or volume of blood transfused.</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; BSA, body surface area; ICU, intensive care unit.

our understanding of how and in what context RAP is most effectively leveraged (25).

DISCUSSION

This current article provides readers with a synthesis of the literature concerning the use and effectiveness of two commonly reported blood conservation strategies. Meta-analyses focusing on the efficacy of ANH appear less than definitive, with a non-significant protective effect of ANH among cardiac surgical patients. Similarly, the efficacy of RAP in reducing transfusion requirements is also less than certain. Findings from our multi-institutional perfusion database suggest that RBC transfusions are quite common among patients undergoing isolated CABG surgery, although rates vary across institutions (26). Using data from PERForm, we report institutional-level variability in use of ANH and RAP; these findings are in keeping with the current low level and class of recommendation from the STS blood management guidelines (6), and suggest uncertainty among clinicians regarding the effectiveness of these strategies.

How do (and should) we manage our patients in the absence of definitive knowledge regarding the efficacy and effectiveness of a given clinical practice? Two strategies come to mind: 1) maintain the status quo and 2) developing and leveraging multi-disciplinary teams to evaluate and continuously improve the quality and safety of care. The former strategy, which will not be advocated by the authors of this manuscript, is akin to burying one’s head in the sand. In contrast, the latter strategy leverages a team-based approach. The use of teams has been previously advocated in part for its role in mitigating errors (27) and more broadly as a necessary ingredient for enabling continuous improvement of health care (28).

Rich and reliable data are the bedrock of effective teams, as they assist in managing uncertainty, assessing the quality of care, and ultimately filling gaps in knowledge. The STS, SCA, and the American Society of Extracorporeal Technology (AmSECT), after reviewing the peer-reviewed literature (6), provided the following recommendation concerning the role of multi-disciplinary teams in blood conservation.

A multi-disciplinary approach involving multiple stakeholders, institutional support, enforceable transfusion algorithms supplemented with point-of-care testing, and all of the already mentioned efficacious blood conservation interventions limits blood transfusion and provides optimal blood conservation for cardiac operations. (Class I, Level of evidence A)

Numerous blood conservation practices were evaluated in these recommendations, including those focused on the pre-, intra-, and post-operative care of patients. As such, one anticipated role of such a team would be the coordination of care across these numerous microsystems (29).

Although the focus of the aforementioned studies was on the utilization of these practices (i.e., ANH and RAP) in real-world settings, future efforts should also understand their contribution to post-operative outcomes. Nonetheless, absent multiple trials supporting the efficacy of ANH or RAP, a number of professional societies further suggest that clinical teams should organize themselves to review and discuss data concerning both processes of care (e.g., RAP use) and outcomes (e.g., transfusion rates). Indeed, members of the AmSECT recently endorsed its most recent update to its professional Standards and Guidelines for perfusionists (30). Of particular relevance, Standard 13 (Quality Assurance and Improvement) states:

Standard 13: The perfusionist shall actively participate in both institutional and departmental quality assurance and improvement programs.

Further, two guidelines underpin this standard:

Guideline 13.1: The perfusionist should collect data concerning the conduct of perfusion via a clinical registry or database.

Guideline 13.2: The perfusionist should use such data for quality assurance and improvement projects.

Otherwise stated, it is our professional obligation to participate in departmental-wide quality assurance and improvement teams. Clinically rich data, similar to what is contained within the PERForm registry, should be used as a foundation for these institutional discussions. It is imperative that data are not only collected, but indeed reported back to multi-disciplinary teams (31).
In conclusion, patients undergoing cardiac surgery continue to be exposed to blood products. A number of blood conservation strategies have been proposed, with varying levels of evidence supporting their efficacy and effectiveness. This uncertainty has likely in part led to center-level differences in the utilization of these practices, including ANH and RAP. Perfusion databases, including the PERForm registry, serve as a vehicle for perfusionists to assess the use and role of these practices within their institution. Nonetheless, these data are mostly likely to be effectively leveraged if used within the context of a multi-disciplinary team, which ultimately has the power to identify and address roadblocks, and support targeted interventions to improve the quality and safety of cardiac surgical care.

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REFERENCES