J Extra Corpor Technol. 2016;48:188–93
The Journal of ExtraCorporeal Technology

The Relationship between Intra-Operative Transfusions and Nadir Hematocrit on Post-Operative Outcomes after Cardiac Surgery

Joshua B. Goldberg, MD;* Kenneth G. Shann, CCP;† David Fitzgerald, CCP;‡ John Fuller, CCP;§ Theron A. Paugh, CCP;¶†† Timothy A. Dickinson, MS, CCP;|| Gaetano Paone, MD, MHSA;** Richard L. Prager, MD;¶†† Donald S. Likosky, PhD;¶†† for the PERForm Registry and the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative

**Westchester Medical Center, New York Medical College, Valhalla, New York; †Division of Cardiac Surgery, Massachusetts General Hospital, Boston, Massachusetts; ‡INOVA Health Systems, Fairfax, Virginia; §St. John Providence Health System Detroit Hospitals, Detroit, Michigan; ¶Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan; ||Specialty Care, Nashville, Tennessee; **Division of Cardiothoracic Surgery, Department of Surgery, Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan; and the ††PERForm Registry and the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative*

Presented at the 53rd American Society of ExtraCorporeal Technology International Conference, Tampa, Florida, April 14–18, 2015.

Abstract: Uncertainty exists regarding the optimal strategy for the management of anemia in the setting of cardiac surgery. We sought to improve our understanding of the role of intra-operative hematocrit (HCT) and transfusions on peri-operative outcomes following cardiac surgery. A total of 18,886 patients undergoing on-pump cardiac surgery were identified from a multi-institutional registry including surgical and perfusion data. Patients were divided into four groups based on their intra-operative nadir HCT (<21 or ≥21) and whether or not they received intra-operative red blood cell (+RBC or −RBC) transfusions. Outcomes were adjusted for the Society of Thoracic Surgeons predicted risk of mortality (PROM), pre-operative HCT, and medical center. Regardless of nadir HCT cohort, those who received a transfusion had higher PROM relative to patients who did not receive a transfusion. The mean PROM was significantly higher among those HCT ≥21 + RBC (5.3%) vs. HCT ≥ 21 − RBC (1.9%), $p < .001$. Similarly, the PROM was significantly higher among HCT <21 + RBC (5.1%) vs. those HCT <21 − RBC (3.1%), $p < .001$. Adjusted outcomes demonstrated an increased impact of RBC transfusions on adverse outcomes irrespective of nadir HCT including stroke ($p < .001$), renal failure ($p < .001$), prolonged ventilation ($p < .001$), and mortality ($p < .001$). This study demonstrates that transfusions have a more profound effect on post-operative cardiac surgery outcomes than anemia. **Keywords:** blood transfusion, cardiopulmonary bypass, outcomes (includes mortality, morbidity). *J Extra Corpor Technol. 2016;48:188–93*

Management of intra-operative anemia in the setting of cardiac surgery remains perhaps one of the most widely debated topics. On one hand, there is convincing evidence associating anemia with a wide range of adverse post-operative outcomes including mortality, stroke, heart failure, renal failure, and infection (1–5). Alternatively, there are a number of reports suggesting transfusions in and of themselves confer similar risk of adverse post-operative sequelae (6–8). In the end, clinicians face uncertainty regarding the optimal strategy for peri-operative management of anemia.

A number of single-center, observational studies have addressed this chicken vs. the egg controversy, the majority of which conclude that anemia and transfusions have synergistic effects on adverse post-operative outcomes (5,8–10). One of the most widely cited studies analyzed data from more than 9,000 patients undergoing cardiac surgery using cardiopulmonary bypass (CPB) from 2004 to 2009 (5). Defining anemia as a hematocrit (HCT) < 25%, the investigators found an additive effect of both anemia and transfusions on adverse post-operative outcomes. However, in its most recent blood management guidelines, the Society of Thoracic

Received for publication July 7, 2016; accepted October 14, 2016.
Address correspondence to: Donald S. Likosky, PhD, Section Head, Section of Health Services Research and Quality, Department of Cardiac Surgery (5346 CVC), University of Michigan Medical School, Ann Arbor, MI 48109-5864. E-mail: likosky@umich.edu
The opinions expressed in this document are those of the authors and do not reflect the official position of the AHRQ or the U.S. Department of Health and Human Services.
Dr. Likosky is supported in part by grant numbers R01HS022535 and R03HS022909 from the Agency for Healthcare Research and Quality (AHRQ). Support for the MSTCVS Quality Collaborative is provided by the Blue Cross and Blue Shield of Michigan and Blue Care Network as part of the BCBSM Value Partnerships program.

Article available at https://ject.edpsciences.org or https://doi.org/10.1051/ject/201648188

Surgeons (STS) suggested an HCT trigger of <21% to guide transfusion decision-making (4). More contemporaneous, multi-center reports have not considered the impact of an HCT trigger of <21% on post-operative sequelae.

In an effort to improve the quality and safety of cardiac surgical care, we analyzed a large multi-center database of both surgical and perfusion practices to improve our understanding of the role of intra-operative HCT and transfusions on peri-operative outcomes following cardiac surgery.

MATERIALS AND METHODS

This study was approved by the institutional review board (IRB) of the University of Michigan Health System (IRB HUM00114960).

Patient Population

The Perfusion Measures and Outcomes (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. The PERForm registry was developed by the International Consortium for Evidence-Based Perfusion, a Committee of the American Society for ExtraCorporeal Technology, and is now organizationally structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). At the time of this publication, 32 of 33 hospitals participating in the MSTCVS-QC contributed data to the PERForm registry, with an additional six centers located outside of Michigan. The MSTCVS-QC began in 2001 as a cardiac surgeon–led quality collaborative embedded in the Michigan Society of Thoracic and Cardiovascular Surgeons, and in 2005, it became partially funded by the Blue Cross/Blue Shield of Michigan. The Collaborative meets quarterly to review various processes and outcomes and to facilitate and evaluate quality improvement studies.

All programs in the MSTCVS-QC use the STS data collection form and submit data on a quarterly basis to both the STS database and the MSTCVS-QC data warehouse. The PERForm registry contains information related to the care and conduct of cardiovascular perfusion practices. (A list of fields and definitions may be found at http://www.mstcvsqualitycollaborative.org/perform-registry.) Each surgical record is merged with a record from the PERForm registry. Participating sites are subject to audits for data validity and accuracy as part of the MSTCVS-QC audit system.

Table 1. Relationships between HCT, transfusions, and pre- and intra-operative characteristics.

Measure	HCT ≥ 21 − RBC	HCT ≥ 21 + RBC	HCT < 21 − RBC	HCT < 21 + RBC	*p* Value
Observations	13,381	2,124	1,216	2,165	
Pre-operative					
PROM (mean, SD)	1.9 (2.7)	5.3 (6.3)	3.1 (3.7)	5.1 (6.1)	<.001
Age (mean, SD)	64.7 (11.0)	69.6 (11.9)	67.5 (11.3)	69.5 (11.6)	<.001
Female (%)	21.3	48.7	54.3	64.6	<.001
BMI (mean, SD)	30.5 (8.8)	28.5 (6.2)	29.5 (13.0)	29.1 (13.1)	<.001
History of stroke (%)	6.7	12.0	8.6	13.0	<.001
Creatinine (mean, SD)	1.1 (.7)	1.5 (1.5)	1.2 (1.1)	1.4 (1.5)	<.001
COPD (%)	11.4	19.2	13.4	17.1	<.001
Diabetes (%)	61.6	57.2	55.4	55.1	<.001
NYHA Class III/IV (%)	12.8	29.5	17.1	27.3	<.001
Recent MI (%)	38.3	44.6	39.6	45.5	<.001
EF (mean, SD)	52.9 (12.6)	50.8 (15.1)	53.9 (12.2)	52.9 (14.0)	<.001
IABP (%)	5.3	8.3	5.4	7.8	<.001
Intra-operative					
Procedure (%)					
Isolated CABG	65.7	43.4	58.7	54.1	
Isolated valve	22.5	29.1	23.8	21.6	
CABG + valve	9.9	21.4	15.6	20.7	
Other	1.9	6.2	1.9	3.7	<.001
Pump time (mean, SD)	105.1 (44.7)	127.3 (68.2)	110.3 (53.8)	130.0 (69.4)	<.001
Clamp time (mean, SD)	80.7 (36.4)	92.7 (50.0)	83.5 (39.5)	95.7 (50.4)	<.001
HCT (mean, SD)					
Pre-operative	39.9 (4.8)	34.2 (5.6)	34.9 (4.9)	33.0 (5.1)	<.001
Last pre-CPB	35.4 (4.7)	28.8 (4.9)	29.2 (3.2)	27.1 (4.2)	<.001
First CPB	28.5 (4.6)	24.3 (3.0)	20.9 (2.7)	19.9 (2.9)	<.001
Nadir CPB	27.2 (4.2)	23.1 (2.3)	19.2 (1.2)	18.4 (1.7)	<.001
Last CPB	28.2 (4.3)	24.7 (2.7)	20.8 (2.3)	22.0 (2.9)	<.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; MI, myocardial infarction; EF, ejection fraction.

Table 2. Relationships between HCT, transfusions, and post-operative complications.

Variables	HCT ≥ 21 − RBC	HCT ≥ 21 + RBC	HCT < 21 − RBC	HCT < 21 + RBC	*p* Value
Observations	13,381	2,124	1,216	2,165	
Stroke					
Crude (%)	1.3	4.0	2.0	3.3	
Adjusted (%)	1.5 (1.2, 1.7)	3.1 (2.1, 4.1)	1.9 (1.1, 2.8)	2.4 (1.6, 3.2)	<.001
Odds ratio*	Ref	2.0 (1.4, 2.8)	1.4 (.8, 2.2)	1.7 (1.2, 2.4)	
Renal failure					
Crude (%)	1.7	6.6	3.0	6.9	
Adjusted (%)	2.2 (1.9, 2.5)	5.2 (3.7, 6.8)	2.8 (1.8, 3.9)	4.8 (3.4, 6.1)	<.001
Odds ratio*	Reference	2.1 (1.6, 2.8)	1.3 (.9, 2.0)	2.2 (1.6, 2.8)	
Prolonged ventilation					
Crude (%)	8.4	26.1	10.9	23.0	
Adjusted (%)	9.7 (.1, 10.2)	18.3 (15.9, 20.7)	10.5 (8.7, 12.4)	16.8 (15.0, 18.6)	<.001
Odds ratio*	Ref	2.2 (1.9, 2.5)	1.1 (.9, 1.4)	2.1 (1.8, 2.4)	
30-day mortality					
Crude (%)	1.6	7.1	3.6	7.2	
Adjusted (%)	1.9 (1.6, 2.2)	5.2 (3.8, 6.5)	3.1 (2.0, 4.1)	4.9 (3.7, 6.1)	<.001
Odds ratio*	Ref	2.5 (1.9, 3.3)	1.6 (1.1, 2.4)	2.6 (2.0, 3.4)	

*Adjusted for PROM, IABP, pre-operative HCT, procedure, and center.

We included all patients ≥18 years of age operated on at 1 of 26 participating medical centers between 2010 and 2014 who underwent one of the following operations: isolated coronary artery bypass grafting (CABG), isolated aortic valve (AVR), AVR + CABG, mitral valve (MV) repair, MV replacement, or CABG + MV repair or replacement. We excluded patients whose procedures do not have a STS predicted risk of mortality (STS PROM) and those with missing information for HCT or transfusion information, patients undergoing off-pump surgery, or surgery for endocarditis. Our final dataset included 18,886 patients.

Measures

The patients were divided into four groups: nadir HCT ≥ 21 without transfusion (HCT ≥ 21 − red blood cell [RBC], *n* = 13,381), nadir HCT ≥ 21 with transfusion (HCT ≥ 21 + RBC, *n* = 2,124), nadir HCT < 21 without transfusions (HCT < 21 − RBC, *n* = 1,216), and nadir HCT < 21 with transfusions (HCT < 21 + RBC, *n* = 2,165). Centers were asked to adhere to the following definition for nadir HCT: "indicate the patient's lowest HCT value by non-continuous measurement (exclude any inline or indwelling values) during the conduct of cardiopulmonary bypass." Centrifugation serves as the preferred method for HCT determination. Intra-operative homologous RBC practices were analyzed along with morbidity (stroke, renal failure, and prolonged ventilation) and 30-day mortality.

Statistical Analyses

The relationship of HCT, intra-operative RBC transfusion, 30-day mortality and morbidity was studied using logistic regression or Poisson models. We adjusted for each patient's predicted risk (using the STS models for mortality or prolonged ventilation), pre-operative HCT, and medical center (11–13). The STS models have been shown to accurately and reliably predict a patient's risk of morbidity and mortality, and are widely used for public

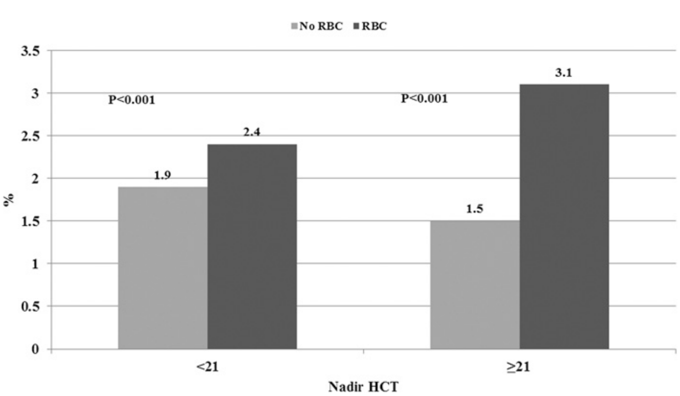

Figure 1. Adjusted stroke rate by strata of nadir HCT. Adjusted for STS predicted risk of stroke, preoperative HCT, and medical center.

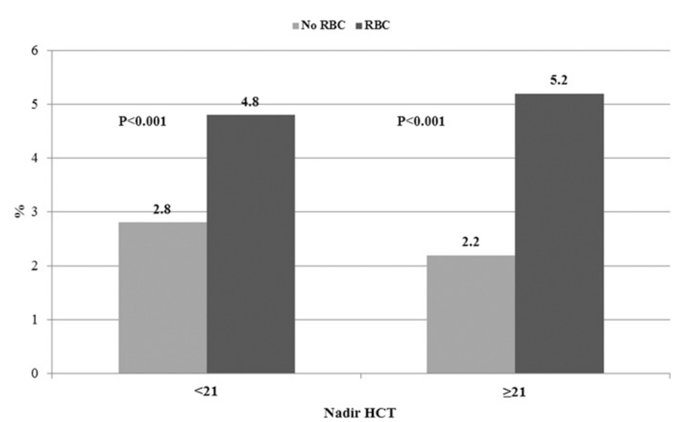

Figure 2. Adjusted renal failure rate by strata of nadir HCT. Adjusted for STS predicted risk of renal failure, preoperative HCT, and medical center.

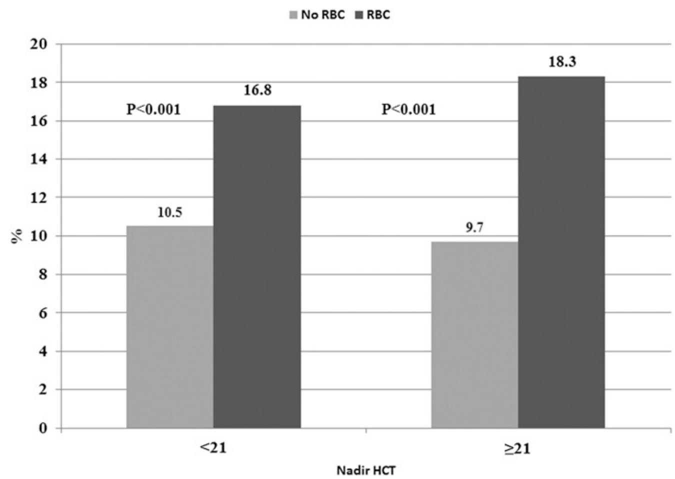

Figure 3. Adjusted prolonged ventilation rate by strata of nadir HCT. Adjusted for STS predicted risk of prolonged ventilation, preoperative HCT, and medical center.

reporting, clinical research, quality assurance, and quality improvement activities (14).

RESULTS

A total of 18,886 patients met inclusion criteria. Basic demographic information is detailed in Table 1. The majority of patients had a nadir HCT ≥ 21 (15,505/18,886, 82.1%). A total of 4,289/18,886 (22.7%) had RBC transfusions. As expected, RBC transfusions were more frequent among patients with nadir HCT < 21 (64% [2,165/3,381] vs. 13.7% [2,124/15,505]) among those with nadir HCT ≥ 21, $p < .05$. Regardless of nadir HCT cohort, those who were transfused had higher PROM relative to patients who were not transfused. The mean PROM was significantly higher among those HCT ≥ 21 + RBC (5.3%) vs. HCT ≥ 21 − RBC (1.9%), $p < .001$. Similarly, the PROM was significantly higher among HCT < 21 + RBC (5.1%) vs. those HCT < 21 − RBC (3.1%), $p < .001$. Patients who received a transfusion were more likely to be older, female and have a pre-operative intra-aortic balloon pump (IABP).

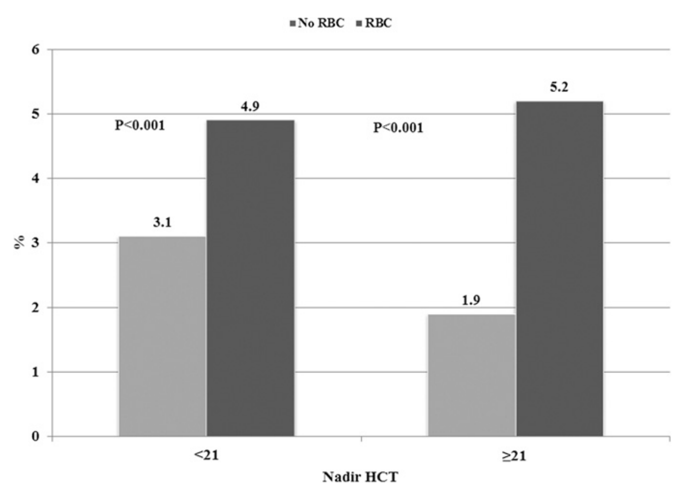

Figure 4. Adjusted 30-day mortality rate by strata of nadir HCT. Adjusted for STS PROM, preoperative HCT, and medical center.

The crude and adjusted post-operative outcomes are detailed in Table 2. There are two general findings when adjusted nadir HCT cohorts are compared (Figure 1). First, transfused patients were associated with increased odds of post-operative sequelae, irrespective of nadir HCT status. Interesting, the adjusted stroke rate was qualitatively similar between patients who did not receive a transfusion (HCT ≥ 21 − RBC 1.5% [confidence interval 95% {CI 95%}: 1.2, 1.7] vs. HCT < 21 − RBC 1.9% [CI 95%: 1.1, 2.8]). However, exposure to RBC transfusions was associated with essentially doubling the adjusted odds of stroke (relative to those with HCT ≥ 21 − RBC) regardless of nadir HCT (HCT ≥ 21 + RBC ORadj2.0 [CI 95%: 1.4, 2.8]; HCT < 21 + RBC ORadj1.7 [CI 95%: 1.2, 2.4]) (Figure 1). A similar finding was noted with post-operative renal failure (Figure 2). Prolonged ventilation occurred more frequently among patients who were transfused, regardless of nadir HCT (Figure 3). Patients who were exposed to RBC transfusions had a higher adjusted rate of mortality relative to those not receiving a transfusion: HCT ≥ 21 − RBC 1.9%; HCT ≥ 21 + RBC 5.2%; HCT < 21 − RBC 3.1%; HCT < 21 + RBC, 4.9%; $p < .001$ (Figure 4).

DISCUSSION

We leveraged a prospectively collected, multi-institution database of both surgical and perfusion practices to analyze the role of intra-operative RBC transfusions on the relationship between intra-operative nadir HCT and post-operative outcomes following cardiac surgery. Our analysis of 18,886 patients demonstrates nadir HCT had minimal associated effect on post-operative outcomes among patients who were not exposed to RBC transfusions. In addition, independent of baseline pre-operative risk, transfusion of RBCs is associated with a more profound increase in patient's risk of post-operative sequelae than anemia alone.

Although there is a large body of literature detailing the isolated adverse effects of anemia or transfusions after cardiac surgery (1,2,4,8), relatively few studies focus on the interaction between both anemia and transfusions on post-operative outcomes. In general, most studies report a synergistic effect of anemia and transfusions on poor post-operative outcomes. Loor et al. in a single-institution series, reported only a slight increase in risk of complications with isolated anemia (HCT < 25) or transfusions without anemia, but a significant increase in adverse outcomes when patients were exposed to both (5). Similarly, Engoren et al. reported that patients exposed to both anemia (Hgb < 12g/dl) and transfusions were more likely to develop post-operative sequelae (9). Habib et al. undertook a single-center study of more than 1,800 patients to assess the effect of anemia (defined as HCT < 22%), transfusions, and CPB duration on post-operative renal function (10). Similar to Loor et al., Habib found exposure to both anemia and transfusions was associated with an additive effect on post-operative renal dysfunction. The only multi-institution study, authored by Surgenor et al. of the Northern New England Cardiovascular Disease Study Group, reported the combination of transfusions and anemia potentiated the risk of low-output failure on their sample of approximately 8,000 patients (8). When adjusting for anemia, Surgenor et al. also reported that transfusions were an independent predictor of post-operative low-output failure (8).

Our study is unique in that it describes a multi-center experience using currently recommended guidelines as a definition of anemia. Unlike the aforementioned findings, our data reflecting a multi-institutional experience suggests transfusions have a much more profound influence on negative post-operative outcomes than anemia alone. Furthermore, our findings are applicable to the current practice environment as our anemia threshold (HCT < 21) is consistent with currently recommended transfusion threshold guidelines (4).

A number of prior studies have highlighted practices that may prevent a patient's exposure to RBC transfusions. For instance, our group has previously reported the benefit of using acute normovolemic hemodilution (ANH); ANH involves removing whole blood prior to heparinization (15). In addition, other practices have been reported, including permissive anemia (16), minimizing prime volume (17), and institutional blood management guidelines (18). Although guidelines exist, their use in actual practice is often quite limited absent a multi-disciplinary collaborative approach (18). Our present findings suggest the importance of developing and implementing institutional approaches toward reducing a patient's exposure to RBC transfusions. Indeed, the STS stressed the importance of such an approach in its most recent blood management guidelines (Class IIa, Level B).

We acknowledge the following limitations to our current study. As with other observational studies, we cannot rule out the effect of unmeasured confounding, including other institutional or physician-related practices. Nonetheless, we used standard statistical approaches, including risk adjustment, to address apparent differences in pre-operative characteristics. Second, while some might argue that HCT < 21 may not appropriately define anemia for a given patient; we chose to adopt this threshold given its inclusion in the most recent STS blood management guidelines. Third, our study focused on the role of HCT and intra-operative transfusions. As such, our findings may not be generalizable to transfusions given outside of the operating room. Fourth, our dataset did not include information concerning the indication and appropriateness of each transfusion decision. We acknowledge that not all transfusions should be avoided, and indeed in many cases transfusions are life preserving.

This analysis of a large multi-institutional database provides insight into the relationship between intra-operative anemia and transfusion practices and their effect on outcomes after cardiac surgery. These findings, along with the existing evidence in the peer-reviewed literature, stress that exposure to RBC transfusions alone may confer a worse outcome to patients than the anemia itself.

REFERENCES

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? J Thorac Cardiovasc Surg. 2003;125:1438–50.
2. Karkouti K, Djaiani G, Borger MA, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg. 2005;80:1381–7.
3. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M. The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. Ann Thorac Surg. 2003;76:784–91; discussion 792.
4. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91:944–82.
5. Loor G, Rajeswaran J, Li L, et al. The least of 3 evils: Exposure to red blood cell transfusion, anemia, or both? J Thorac Cardiovasc Surg. 2013;146:1480–7. e1486.
6. Koch CG, Khandwala F, Li L, Estafanous FG, Loop FD, Blackstone EH. Persistent effect of red cell transfusion on health-related quality of life after cardiac surgery. Ann Thorac Surg. 2006;82:13–20.
7. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med. 2006;34:1608–16.
8. Surgenor SD, DeFoe GR, Fillinger MP, et al. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. Circulation. 2006;114(Suppl):I43–8.
9. Engoren M, Schwann TA, Habib RH, Neill SN, Vance JL, Likosky DS. The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014;97:514–20.
10. Habib RH, Zacharias A, Schwann TA, et al. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome. Crit Care Med. 2005;33:1749–56.
11. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 2–isolated valve surgery. Ann Thorac Surg. 2009;88(Suppl):S23–42.
12. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 1–coronary artery bypass grafting surgery. Ann Thorac Surg. 2009;88(Suppl):S2–22.

13. Shahian DM, O'Brien SM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: Part 3–valve plus coronary artery bypass grafting surgery. Ann Thorac Surg. 2009;88(Suppl): S43–62.
14. National Quality Forum. National Voluntary Consensus Standards for Cardiac Surgery. A Consensus Report, Washington, DC. 2004.
15. Goldberg J, Paugh TA, Dickinson TA, et al. Greater volume of acute normovolemic hemodilution may aid in reducing blood transfusions after cardiac surgery. Ann Thorac Surg. 2015;100:1581–7; discussion 1587.
16. Moskowitz DM, McCullough JN, Shander A, et al. The impact of blood conservation on outcomes in cardiac surgery: Is it safe and effective? Ann Thorac Surg. 2010;90:451–8.
17. Cormack JE, Forest RJ, Groom RC, Morton J. Size makes a difference: Use of a low-prime cardiopulmonary bypass circuit and autologous priming in small adults. Perfusion. 2000;15:129–35.
18. Likosky DS, Surgenor SD, Dacey LJ, et al. Rationalising the treatment of anaemia in cardiac surgery: Short and mid-term results from a local quality improvement initiative. Qual Saf Health Care. 2010;19:392–8.