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Net Prime Volume Is Associated with Increased Odds of Blood Transfusion

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Abstract: Hemodilutional anemia has been cited as a contributing factor to red blood cell (RBC) transfusions in cardiac surgery patients. Accordingly, efforts have been made to minimize hemodilution by reducing cardiopulmonary bypass (CPB) prime volume. We sought to assess the impact of these efforts on intraoperative RBC transfusions. We evaluated 21,360 patients undergoing coronary artery bypass with or without aortic valve surgery between July 2011 through December 2016 at any of 42 centers participating in the Perfusion Measures and Outcomes registry. The primary exposure was net CPB prime volume (total prime volume minus retrograde autologous prime volume) indexed to body surface area (mL/m^2), which was further divided into quartiles (Q1: <262 mL/m^2, Q2: 262–377 mL/m^2, Q3: 377–516 mL/m^2, and Q4: >516 mL/m^2). The primary outcome was intraoperative RBC transfusion. We modeled the effect of index net prime volume on transfusion, adjusting for patient (age, gender, race, diabetes, vascular disease, previous myocardial infarction, ejection fraction, creatinine, preoperative hematocrit (HCT), total albumin, status, aspirin, and antiplatelet agents), procedural (procedure types) characteristics, surgical year, and hospital. The median net prime volume was 378 mL/m^2 (25th percentile: 262 mL/m^2, 75th percentile: 516 mL/m^2). Relative to patients in Q1, patients in Q4 were more likely to be older, female, nondiabetic, have higher ejection fraction, have more ultrafiltration volume removed, and undergo more elective and aortic valve procedures (all $p < .05$). Patients in Q4 relative to Q1 were exposed to lower nadir HCTs on bypass, $p < .05$. The net prime volume was associated with an increased risk of transfusion (8.9% in Q1 vs. 22.6% in Q4, $p < .001$). After adjustment, patients in Q4 (relative to Q1) had a 2.9-fold increased odds (OR_{adj} = 2.9, 95% CI [2.4, 3.4]) of intraoperative RBC transfusion. In this large, multicenter experience, patients exposed to larger net prime volumes were associated with greater adjusted odds of receiving intraoperative transfusions. Our findings reinforce the importance of efforts to reduce the net CPB prime volume. Based on these findings and other supporting evidence, the net prime volume should be adopted as a national quality measure. **Keywords:** cardiopulmonary bypass (CPB), blood transfusion, CPB circuit prime volume. *J Extra Corpor Technol. 2019;51:195–200*

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Prior work has demonstrated that cardiac surgery patients exposed to red blood cell (RBC) transfusions are at increased odds of developing short- and long-term morbidity and mortality (1–3). As a result, blood conservation guidelines have been established to identify modifiable factors to decrease blood transfusions (4–7). Cardiopulmonary bypass (CPB) circuit prime has been a specific focus of blood conservation guidelines, given the hemodilution that results from a relatively large volume of asanguinous fluid within the prime.

CPB circuit prime volume is the amount of asanguinous fluid (crystalloid and/or colloid in milliliters) it takes to prime- or fluid-fill the entire circuit that typically includes the venous and arterial lines, venous reservoir, oxygenator, arterial filter, and cardioplegia circuit). The current Society of Thoracic Surgeon (STS) blood conservation guidelines recommend minimizing CPB circuit prime volume as an integral evidenced-based (Class I, Level A) strategy to reduce blood transfusions by decreasing hemodilutional anemia. In part related to these guidelines, a number of studies have been published (8–11) documenting institutional efforts, focusing on reducing CPB circuit prime volumes. Previous studies (8–11) have demonstrated that reducing the size of the CPB circuit and related prime volume may help to minimize hemodilution and subsequent RBC transfusions. However, few studies have evaluated the incremental impact of prime volume on patient exposure to RBC transfusion.

In an effort to improve the quality and safety of cardiac surgery patients, we used the Perfusion Measures and Outcomes (PERForm) registry to assess efforts aimed at reducing intraoperative RBC exposures by minimizing CPB prime volume.

METHODS

This study was approved by the Institutional Review Board of the University of Michigan.

Patient Population

The PERForm registry is organizationally structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). The MSTCVS-QC began in 2001 as a cardiac surgeon-led quality collaborative embedded in the MSTCVS, and, in 2005, it became partially funded by the Blue Cross/Blue Shield of Michigan insurance company. The collaborative meets quarterly to review various processes and outcomes, and to facilitate and evaluate quality improvement studies. Recently, the PERForm registry signed a memorandum of understanding with the American Society of ExtraCorporeal Technology (AmSECT), whereby AmSECT recognizes the PERForm registry as its official registry, and, in turn, the PERForm registry recognizes AmSECT as its official societal partner.

All programs in the MSTCVS-QC use the STSs data collection forms 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.performregistry.org.) Each surgical record is merged with a record from the PERForm registry (12). Participating centers are audited routinely for data validity and accuracy as part of the MSTCVS-QC audit system.

We included all patients who underwent coronary artery bypass with or without aortic valve surgery between July 2011 through December 2016 at any of the 42 centers participating in the PERForm registry. Patients who underwent procedures other than coronary artery bypass graft or aortic valve replacement (AVR) had off-pump cardiac surgery, had preoperative or intraoperative mechanical support devices (including an intra-aortic balloon pump, ventricular assist device, and extracorporeal membrane oxygenation), were admitted as emergent or emergent salvage, previously had cardiovascular surgery, had endocarditis, received dialysis before surgery, and were excluded from this study. After exclusion, 21,360 patients were included in the analysis.

Measures

The primary exposure was the net prime volume indexed to the patient's body surface area (BSA) (mL/m^2), "index net prime volume." The net prime volume was calculated by the total prime volume minus any retrograde autologous prime (RAP) volume. The index net prime volume was further divided into quartiles after accounting for the patient's BSA (Q1: $\leq$262, Q2: 262–377, Q3: 377–516, and Q4: $>$516 mL/m^2). The primary outcome was intraoperative RBC transfusion.

We additionally report as many of AmSECT's mandatory data elements reflecting CPB-related contributions to RBC transfusions (13). Each of these data elements is signified by a "+" sign in Table 1. These data elements represent the culmination of discussions and consensus regarding the minimum criteria for reporting on CPB-related contributions to RBC transfusions in the setting of adult cardiac surgery. The eAppendix details which of these mandatory measures are included (reported) in the PERForm registry.

Statistical Analyses

Categorical variables were presented as percentages and continuous variables were presented as median (interquartile) in the univariate analysis table. Chi-square and Fisher exact tests were used to test statistical

Table 1. Preoperative characteristics by quartiles of net prime volume indexed to patient body surface area.

Variable	RBC Criteria	Q1 <262 mL/m² Value	Q1 % or IQR	Q2 262–377 mL/m² Value	Q2 % or IQR	Q3 377–516 mL/m² Value	Q3 % or IQR	Q4 >516 mL/m² Value	Q4 % or IQR	Q1 vs. Q4 *p* Value
Number of procedures	–	5,344	–	5,322	–	5,354	–	5,340	–	–
Number of centers	–	39	–	40	–	42	–	42	–	–
Demographics										
Age (years)	+	66	58, 73	66	59, 74	67	60, 74	68	60, 76	<.0001
Female	+	1,158	21.7	1,302	24.9	1,417	26.5	1,873	35.1	<.0001
BSA	+	2.13	1.95, 2.31	2.07	1.91, 2.25	2.04	1.89, 2.21	1.98	1.80, 2.15	<.0001
Cardiac history										
Previous myocardial infarction	–	2,320	43.4	2,229	41.9	2,148	40.1	2,132	39.9	.0002
Hypertension	–	4,800	89.8	4,749	89.2	4,711	88	4,643	86.9	<.0001
PAD	–	745	13.9	733	13.8	752	14	692	13	.14
Risk factors										
Diabetes	–	2,511	47	2,354	44.2	2,328	43.5	2,106	39.4	<.0001
Last creatinine	–	1	.8, 1.13	.99	.8, 1.14	.99	.8, 1.14	.95	.8, 1.12	.002
HCT, last preoperative	+	40	36.4, 43.0	40.1	36.8, 43.0	40	36.6, 43.0	39.3	36.0, 42.6	<.0001
Ejection fraction	–	56	48, 60	56	48, 60	56	50, 62	58	50, 63	<.0001
STS risk of major morbidity and mortality	+	.01	.006, .021	.01	.006, .022	.01	.006, .022	.01	.007, .024	<.0001
Medications										
Aspirin within 5 days	–	4,644	86.9	4,566	85.8	4,590	85.7	4,422	82.8	<.0001
Antiplatelets with 5 days	–	348	6.5	289	5.4	245	4.6	208	3.9	<.0001
Coumadin within 24 hours	–	16	.3	36	.7	22	.4	20	.4	.61
Acuity										<.0001
Elective status	+	2,654	49.7	2,781	52.3	2,983	55.7	2,954	55.3	–
Urgent	+	2,690	50.3	2,541	47.7	2,370	44.3	2,385	44.7	–

Value is the "n" for categorical data and the median for continuous data. % is for categorical data and IQR (interquartile range) is for continuous data.

significance for categorical variables. Wilcoxon rank-sum tests were used for continuous variables.

Missing values of categorical variables with less than 1% missingness were imputed with their lowest risk values. Missing values of continuous variables were imputed to the mean.

We modeled the effect of the index net prime volume on RBC transfusion using a multivariable logistic model, adjusting for age, gender, race, diabetes, prior stroke, hypertension, cardiovascular disease, peripheral arterial disease (PAD), previous myocardial infarction, ejection fraction, creatinine, last preoperative hematocrit (HCT), and total albumin, status; the use of aspirin, Coumadin®, and adenosine diphosphate receptor inhibitor medication; procedure types; surgical year; and hospital as fixed effect. For testing, p values of less than .05 (two-tailed) were considered statistically significant. All statistical calculations used R version 3.4.0 and SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 21,360 patients were analyzed with an overall median net prime volume of 378 mL/m^2 (25th percentile: 262 mL/m^2 and 75th percentile: 516 mL/m^2). Crude demographic data stratified by indexed net prime quartiles are detailed in Table 1. Relative to patients in the first quartile (Q1), patients in the fourth quartile (Q4) were more likely to be older, be female, have a smaller BSA, have higher ejection fraction, less likely to receive antiplatelet agents within 5 days of surgery, and undergo urgent operations (all $p < .05$; Table 1). Several of these variables, however, have small absolute differences, including age (2 years), and ejection fraction (2%).

Patients in Q4, relative to Q1, were more likely to undergo aortic valve operations, $p < .05$. Nonetheless, patients in Q4 were less likely to receive retrograde autologous priming and acute normovolemic hemodilution (ANH), and had shorter pump and cross clamp times (all $p < .05$; Table 2). HCT values were qualitatively similar at baseline, although the first intraoperative HCT was higher in absolute terms by 3% (38% vs. 35%) for patients in Q1 vs. Q4, $p < .05$. This absolute difference in HCT persisted to the first HCT on bypass (28% vs. 25%), all $p < .05$.

Increasing quartiles of the net prime volume was associated with an increased adjusted risk of transfusion (Q1: 10.2% vs. Q4: 18.4%; Figure 1). After adjustment, patients in Q2 had a 27% increased odds of transfusion (OR_{adj} 1.27, $p = .004$) relative to patients in Q1, those in Q3 had a 76% increased odds (OR_{adj} 1.76, $p < .001$), whereas those in Q4 had a 2.9-fold increased odds (OR_{adj} 2.88, $p < .001$; Table 3). Increasing indexed prime volume was associated with an increased adjusted risk for anemia (defined as nadir

Table 2. Intra- and postoperative characteristics by quartiles of net prime volume indexed to patient body surface area.

Variable	RBC Criteria	Q1 <262 mL/m^2		Q2 262–377 mL/m^2		Q3 377–516 mL/m^2		Q4 >516 mL/m^2		Q1 vs. Q4 *p* Value
		Value	% or IQR	Value	% or IQR	Value	% or IQR	Value	% or IQR	
Number of procedures	–	5,344	–	5,322	–	5,354	–	5,340	–	–
Number of centers	–	39	–	40	–	42	–	42	–	–
Intraoperative procedure										<.0001
CABG	–	4,047	75.7	3,911	73.5	3,915	73.1	3,849	72.1	
CABG + AVR	–	523	9.8	553	10.4	600	11.2	609	11.4	
AVR	–	774	14.5	858	16.1	839	15.7	882	16.5	
RAP										
Use	+	5,294	99.1	5,172	97.2	4,664	87.1	2,455	46	<.0001
Volume (mL, among usage)	+	600	550, 800	600	400, 700	500	400, 650	400	250, 500	<.0001
ANH										
Use	–	1,376	25.7	909	17.1	700	13.1	517	9.7	<.0001
Volume (mL, among usage)	–	450	450, 900	600	450, 900	450	400, 900	500	450, 900	.60
Ultrafiltration										
Use	+	1,148	21.8	1,169	22.3	1,287	24.4	1,171	22.2	.58
Volume (mL, among usage)	+	450	450, 900	600	450, 900	450	400, 900	500	450, 900	.60
Static ECC prime volume	–	900	800, 1,085	1,000	900, 1,200	1,200	1,000, 1,338	1,200	1,000, 1,300	<.001
Total volume added (mL)	–	900	520, 1,629	1,120	600, 1,900	1,001	539, 1,865	1,000	500, 1,865	.001
Pre-CPB crystalloid volume (mL)	+	1,000	750, 1,400	1,000	700, 1,200	906	700, 1,200	1,000	700, 1,400	.53
Intraoperative RBC transfusion	+	477	8.9	568	10.7	718	13.4	1,207	22.6	<.001
Pump time (minutes)	+	101	78, 129	101	79, 129	98	78, 126	90	68, 120	<.0001
Cross-clamp time (minutes)	+	78	59, 101	77	59, 100	76	59, 100	71	54, 95	<.0001
HCT										
First intraoperative HCT	+	38	34, 41	37	34, 41	37	33, 41	35	32, 39	<.0001
Last pre-CPB HCT	+	35	31, 38	35	31, 39	35	31, 39	34	30, 37	<.0002
First HCT on CPB	+	28	24, 32	28	24, 31	27	24, 31	25	22, 28	<.0003
Lowest HCT on CPB	+	27	23, 30	26	23, 30	26	23, 30	24	21, 27	<.0004
Last HCT on CPB	+	27	24, 31	27	24, 31	27	24, 31	26	23, 28	<.0005
First HCT in ICU	+1	31	28, 35	31	28, 35	31	28, 35	29	26, 33	<.0006

Value is the "n" for categorical data and the median for continuous data. % is for categorical data and IQR (interquartile range) is for continuous data ICU, intensive care unit.

HCT on CPB ≤21, Table 4. Each 100 mL increase in the net prime volume was associated with a 17% increased adjusted odds for nadir HCT on CPB ≤21 (OR_{adj} 1.17, $p < .001$).

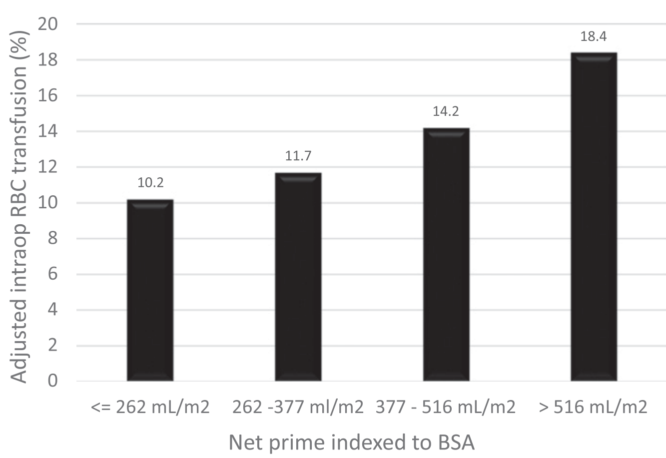

Figure 1. Adjusted relationship between quartiles of net prime volume per body surface area and red blood cell transfusions. Adjusted for age, gender, race, diabetes, prior stroke, hypertension, cardiovascular disease, PAD, previous myocardial infarction, ejection fraction, creatinine, last preoperative HCT, total albumin, and status; the use of aspirin, Coumadin, and adenosine diphosphate inhibitor medication; procedure types; surgical year; and hospital as fixed effect.

DISCUSSION

We used a prospectively collected, multi-institutional database of both surgical and perfusion practices to analyze the role of minimizing the net CPB prime volume on intraoperative RBC transfusion. Our analysis of 21,360 patients demonstrates that increasing the net prime volume indexed to the patient's BSA was associated with an increased adjusted odds of intraoperative RBC transfusion (Q1: 10.2% vs. Q4: 18.4%). In addition, increasing the indexed net prime volume was associated with a decrease in the lowest nadir HCT on CPB (absolute difference of 3.0, Q4 vs. Q1).

We acknowledge the following limitations to our present study. As with other observational studies, we cannot rule out the effect of unmeasured confounding factors, including other institutional (e.g., blood management teams) or physician-related determinants (e.g., transfusion triggers) (14). Nonetheless, we used standard statistical approaches, including risk adjustment, to address commonly reported and tracked preoperative characteristics in addition to the particular operation performed, year of procedure, and cardiac surgical center. In addition, our study solely focused on the role of the indexed net prime volume on intraoperative RBC transfusion. As such, our findings may not impact the patient's overall exposure to

Table 3. Relationship between quartiles of net prime volume per body surface area and adjusted odds for intraoperative transfusion.

Net Prime/BSA Quartile	Crude			Adjusted		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Quartile 1 (≤262 mL/m^2)	Ref			Ref		
Quartile 2 (262–377 mL/m^2)	1.22	1.07, 1.39	.002	1.27	1.08, 1.49	.004
Quartile 3 (377–516 mL/m^2)	1.58	1.39, 1.79	<.0001	1.76	1.48, 2.09	<.0001
Quartile 4 (>516 mL/m^2)	2.98	2.66, 3.34	<.0001	2.88	2.41, 3.44	<.0001

Adjusted for age, gender, race, diabetes, prior stroke, hypertension, cardiovascular disease, peripheral arterial disease, previous myocardial infarction, ejection fraction, creatinine, last preoperative HCT, total albumin, and status; the use of aspirin, Coumadin, and adenosine diphosphate inhibitor medication; procedure types; surgical year; and hospital as fixed effect.

RBC transfusion (e.g., postoperative RBC transfusions). Although we present findings from a large, multicenter experience, we recognize that our findings are only generalizable to centers participating in the PERForm registry.

A body of evidence suggests a reduction in prime volume is useful adjunct for minimizing RBC transfusion (8–11). In addition, the STS', Society of Cardiovascular Anesthesiologists, and the International Consortium for Evidence-Based Perfusion recommend minimizing prime volume as an integral, evidence-based (Class I, Level A) blood conservation practice (4). Despite this recommendation, our present study and others demonstrate the wide variability in the amount of the net prime volume used. Continued variability in practice may be attributed in part to a lack of professionally based standards regarding prime volumes necessary for reducing a patient's exposure to RBC transfusion (15).

Body size and gender have been demonstrated to be important and nonmodifiable determinants for increased exposure to RBC transfusion during cardiac surgery (16–17). In an observational study of 1,235 consecutive patients undergoing primary coronary artery bypass grafting (CABG) surgery, Scott et al. (16) revealed that female gender and lower body weight were associated with an increased odds (OR_{adj} 2.37 and 2.18, respectively, $p < .001$) of receiving RBC transfusion. Similarly, our study demonstrated that patients in Q4: >516 mL/m^2 had a 2.9-fold increased adjusted odds (OR_{adj} 2.88, $p < .001$) or intraoperative RBC transfusion relative to patients in Q1: ≤262 mL/m^2. Patients in the highest quartile were more likely to be female and have smaller BSA. Cardiac teams may wish to consider minimizing net prime volumes within this particular patient subgroup to reduce intraoperative RBCs. The work by Bronson and coworkers demonstrated that by individualizing or "right sizing" the CPB circuit based on the patient's size (and blood flow requirements), they were able to significantly decrease RBC transfusions (10).

Table 4. Relationship between quartiles of net prime volume per body surface area and for lowest HCT on bypass lower or equal to 21.

Net Prime/BSA Quartile	Adjusted OR	95% CI	*p* Value
Quartile 1 (≤262 mL/m^2)	Ref		
Quartile 2 (262–377 mL/m^2)	1.38	1.19, 1.59	<.0001
Quartile 3 (377–516 mL/m^2)	1.71	1.47, 1.99	<.0001
Quartile 4 (>516 mL/m^2)	2.30	1.96, 2.70	<.0001
100 unit of increased indexed net prime volume	1.17	1.14, 1.21	<.0001

Adjusted for age, gender, race, diabetes, prior stroke, hypertension, cardiovascular disease, peripheral arterial disease, previous myocardial infarction, ejection fraction, creatinine, last pre-operative HCT, total albumin, and status; the use of aspirin, Coumadin, and adenosine diphosphate inhibitor medication; procedure types; surgical year; and hospital as fixed effect.

The largest net prime volume group (Q4) had a 2.3-fold increase in exposure to nadir HCT on CPB ≤21%. Nadir HCT "cutoff" of 21% was chosen based on current STS blood conservation guidelines that recommend maintaining a hemoglobin level ≥7 gm/dL in patients on CPB (4). Prior work has documented the relationship between nadir intraoperative HCT and increased odds of RBC transfusion (18–19). Furthermore, transfusions may have a more profound adverse effect on postoperative cardiac surgery outcomes than anemia (20–23). Therefore, blood management efforts should be mainly directed to avoiding anemia by preserving red cell mass, thereby decreasing the need for subsequent RBC transfusions and worsening outcomes. Reducing CPB net prime volume is a vital blood management practice that will help minimize intraoperative anemia, thereby decreasing the likelihood that a decision has to be made as to whether to provide a subsequent and perhaps unnecessary RBC transfusion to a patient.

This analysis of a large multi-institutional database provides insight into the relationship between indexed prime volume and intraoperative RBC transfusions. These findings, along with existing evidence in the peer-reviewed literature and blood conservation guidelines, stress the importance of minimizing the indexed net prime volume and adhering to existing related blood conservation guidelines. Further work needs to be done to better define the appropriate or optimal indexed prime volume for a given patient to minimize intraoperative RBC exposure. Greater participation in a societal perfusion database/registry may help determine optimal prime volume in adult cardiac surgery and have a greater understanding on the factors that impact intraoperative RBC transfusion and nadir HCT. Furthermore, the results found in this study may serve as the foundation for initiating and guiding targeted local quality improvement activities.

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