Intraoperative Blood Collection Without Fluid Replacement for Cardiac Surgery – A Retrospective Analysis

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INTRODUCTION

Blood transfusion with cardiac surgery accounts for 20% of transfusions in the United States. While restrictive transfusion thresholds have been shown to produce equivalent outcomes as liberal thresholds, the overall transfusion rate remains high. Transfusions are not benign. They are associated with increased morbidity and mortality. The hemodilution resulting from crystalloid priming of the cardiopulmonary bypass (CPB) circuit represents a major risk factor for blood transfusions. While several techniques are available to limit hemodilution, such as retrograde autologous priming and high-volume ultrafiltration, these may be insufficient to prevent transfusions. Additionally, the abnormal conditions

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of blood subjected to the various components of the CPB circuit can lead to platelet dysfunction and destruction.\[4\] The resulting thrombocytopenia or functional thrombocytopenia contributes to postoperative coagulopathy and hemorrhage, with frequent need for erythrocyte (RBC) and platelet transfusions. To minimize the need for transfusions and their associated risk of infection, acute lung injury, and immunomodulation, some physicians use intraoperative blood collection.\[6-13\] After induction of general anesthesia, blood is sterilely removed from the patient and stored in bags containing CPDA as a preservative and anticoagulant.\[8,9,12\]

When RBC are removed for intraoperative blood collection, platelets and clotting factors are also captured for reinfusion after discontinuation of CPB. Putatively, this technique conserves blood by decreasing postoperative coagulopathy and the need for transfusions by providing a sufficient quantity of fresh platelets and clotting factors to replace the ones activated or consumed during CPB.\[14\] However, platelet function was adversely affected by storage in CPDA\[15\] and did not improve thromboelastography values after CPB.\[16\] Studies of autologous blood removal primarily used crystalloid or colloids to replace the blood volume [acute normovolemic hemodilution (ANH)].\[9,15,17\]

This can lead to hemodilution of platelets, clotting factors, and RBC and increase the risk of homologous RBC transfusion to prevent or treat low oxygen delivery or hemodynamic instability. Instead of crystalloid or colloid infusions to maintain intravascular volume and hemodynamics, hemodynamics can also be maintained with vasopressors. The use of vasopressors and minimizing volume administration [autologous blood removal without fluid replacement (AWOF)] is designed to limit hemodilution and the need to transfuse homologous RBC.

We hypothesized that AWOF would be associated with decreased blood transfusion requirements in a dose-dependent manner. We further hypothesized, as secondary outcomes, that AWOF would be associated with increased vasopressor requirements, no differences in metabolic (acid–base) parameters, no difference in rate of acute kidney injury (AKI), and higher hematocrit and platelet levels on arrival in the intensive care unit.

METHODS

Ethics

This study was approved by the institutional review board, which waived informed consent as it was a retrospective analysis and it was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 2000. STROBE guidelines were used. All adult patients (age ≥18 years) undergoing cardiac surgery between Jan 31, 2007 and Nov 6, 2013 were included in the study. Patients undergoing ventricular assist device surgery, heart transplants, or cardiac surgery without cardiopulmonary bypass were excluded.

Patient management

Fluids (including infusions and cardioplegia, but excluding piggyback and push medicines), blood products, and vasopressors administered by the anesthesiologist or the perfusionist are recorded in the shared electronic anesthetic record (Centricity, GE Healthcare, Chicago, IL) and were abstracted from it. Laboratory values were extracted from the institutional data warehouse. AKI was defined using Kidney Disease: Improving Global Outcomes (KDIGO) stages: creatinine increase >0.3 mg/dL over 48 hours or to 150% of baseline by day 7 was stage 1; creatinine to >200% of baseline was stage 2, and >300% of baseline was stage 3. Urine output was not included in our outcome definition. Hematocrit levels were determined preoperatively, postinduction before blood was removed, postblood removal but prebypass, and 30 minutes after arrival in the ICU. The lowest intraoperative arterial pH and bicarbonate and highest lactic acid level were used as measures of worst metabolic derangement.

Patients routinely received general anesthesia with midazolam, fentanyl, propofol, and a neuromuscular blocker for induction. Etomidate was rarely used. In addition to routine EKG and pulse oximetry, patients had an arterial line and either a central venous catheter or pulmonary artery catheter. Mechanical ventilation with $V_T = 6–8 \text{ mL/kg}$ of predicted body weight, with rate adjusted to achieve normocarbia was used. PreCPB, intravenous fluids, usually lactated ringer’s solution, were minimized. Hetastarch was not used. Vasopressors were used as necessary to maintain mean arterial pressure >65 mmHg. Bolus ephedrine and phenylephrine and phenylephrine and norepinephrine infusions were used to support hemodynamics. As needed, vasopressin or epinephrine was used. After establishment of central venous access, an antifibrinolytic infusion was started and continued until shortly before leaving the operating room. Initially, aprotinin (2,000,000 KIU load, followed by infusion at 500,000 KIU/hour for the duration of the operation and a pump prime of 2,000,000 KIU) was used. After its removal from the market, we used aminocaproic acid (70 mg/kg load followed by infusion at 30 mg/kg/hr for the duration of the operation). Tranexamic acid was used when aminocaproic acid was in shortage (8 mg/kg load followed by infusion at 4 mg/kg/hr for the duration
of the operation. If creatinine was 1.6-3.3 mg/dL, the tranexamic acid infusion was 3 mg/kg/hour. If creatinine was 3.4-6.6 mg/dL, the infusion was 2 mg/kg/hr. For creatinine >6.6. mg/dL or receipt of dialysis, the infusion was 1 mg/kg/hr. Additionally, 0.6 mg/kg load was added to the bypass circuit.) The decision for removal and amount of autologous blood removal was decided jointly by the surgeon and anesthesiologist. After preparation with chlorhexidine or povidone-iodine, autologous blood was aseptically removed via the central venous access and stored in bags prefilled with CPDA anticoagulant. Bags were not routinely weighed but filled based on visual inspection. Blood was stored at room temperature and gently agitated before being transfused. Prior to cardiopulmonary bypass, heparin 300 U/kg was administered intravenously. The CPB circuit was primed with 900 – 1100 mL of fluid, usually PlasmaLyte. If autologous priming was not used, an additional 300 – 500 mL of fluid was added to the bypass circuit. These volumes were recorded on the anesthetic record and included in the fluid analyses. Mild (32-35°C) or moderate (28-31°C) hypothermia was employed on bypass, with sweeps adjusted to maintain PaCO₂ = 40 mmHg[18]. Deep (≤25°C) hypothermia was used with circulatory arrest.[18] Additional heparin doses were given to keep the activated clotting time >400 sec. After separation from CPB, heparin was reversed with protamine (1-1.3 mg per 100 units of initial heparin dose) and confirmed by ACT returning to baseline values. Additional doses of protamine could be given if the ACT was elevated. Heparin concentration assays were not used. After reversal of heparin, the autologous blood was transfused. Physical measures of thrombosis, such as thromboelastography, were not employed. RBC transfusions were based on hematocrit levels (over the study period, the transfusion trigger for RBC decreased from 22-24% to ~18%) and clinical judgment, which included hemodynamics. Plasma, platelet, and cryoprecipitate transfusions were based on clinical judgment, inspection of the surgical field, and, when available, laboratory tests.

Power analysis
Based on current practice, we assumed that 20% of patients have no autologous blood removed and that intraoperative transfusion rate is 20%, then to find a 3% change, an amount for which we would consider changing our practice, in the transfusion rate to 17 or 23% in patients who have any autologous blood removed, with alpha = 0.05 and power = 0.8, would require 4000 subjects.

Statistical analysis
Baseline characteristics were described with means (standard deviations), medians (interquartile range), frequency, and percentages. Differences in categories were tested using one-way ANOVA, the Kruskal–Wallis test, or the Chi-square test. To determine the independent associations of autologous blood removal with outcomes, we used Akaike Information Criteria based linear and logistic regressions. We further analyzed the data using propensity matching. Here, nonparsimonious binary logistic regression using sex, age, ASA class, emergency status, surgery type, type of surgery, type of antifibrinolytic used, height, weight, body mass index, body surface area, platelet count, INR, creatinine, and postinduction hematocrit value was used to calculate a propensity to be in the AWOF group. AWOF patients were matched to Control patients by similar propensity scores using a nearest neighbor greedy algorithm. The match was considered successful if all variables had standardized differences <10%. All analyses were performed with R version 2.14.2 (R Foundation for Computing, Vienna, Austria). Linear regression results are presented as estimate B (95% confidence interval) and logistic regressions as adjusted odds ratio (aOR) (95% confidence interval). As the dose-response (outcome associated with the number of autologous blood units removed) might be nonlinear or have a threshold, we analyzed number of autologous units as a categorical variable in all regressions.

Sensitivity analysis
The main analyses were done adjusting for albumin volume in a 3:1 ratio for 5% and 15:1 ratio for 25% as is traditionally considered.[9] As more recent research has suggested that equal volumes of albumin and crystalloid produce equal expansions of blood volume,[20] we did sensitivity analyses of all regressions using unadjusted volumes.

RESULTS
We studied 2809 patients, 61 ± 15 years old, 1874 (67%) male, with body mass index 29.5 ± 6.3 kg/m². The preoperative hematocrit was 39.0 ± 5.4%. Five hundred ninety-six patients (21%) had no blood removed (Control group), whereas 482 (17%), 1257 (45%), and 474 (17%) AWOF patients had 1, 2, or 3 units of blood removed, respectively. AWOF patients had higher preoperative hematocrits, but lower creatinine levels and platelet counts [Table 1]. After anesthesia induction and before blood removal, AWOF patients had higher hematocrits than the Control group, but the postinduction hematocrit did not differ within the AWOF group by number of units removed [Table 1].

Processes of care
Intravenous fluid administration was less in AWOF group with one unit removed compared to Control
patients. Only when three units were removed, was intravenous fluid administration greater [Table 1]. The number of boluses of vasopressor doses was statistically, but not clinically, significantly higher in the AWOF group, 10.5 (5,17), 10 (5,16), and 13 (8,19) for AWOF = 1, 2, and 3, respectively, \( P < 0.001 \). Total phenylephrine dose was greater, but epinephrine and norepinephrine doses were less in the AWOF groups [Table 2]. While there were slight differences in nadir intraoperative pH and bicarbonate among the four groups, overall, there was no trend between pH, bicarbonate, and groups \( P = .744 \) and. 128, respectively). Similarly, while lactic acid levels were lower in AWOF patients with one \( 2.6 \pm 1.4 \text{ mmol/L} \) and two \( 3.0 \pm 1.8 \text{ mmol/L} \) units removed compared to Control \( 3.6 \pm 2.6 \text{ mmol/L} \), \( P < .001 \) and. 005, respectively, there was no overall trend in lactic acid levels with the number of blood units removed \( P = .410 \) [Table 3].

By multivariable linear regression, AWOF patients had similar or slightly better nadir pH, nadir bicarbonate, and peak lactic acid levels then Control patients [Table 4]. Using multiple linear regression to adjust for other demographics, preoperative laboratory values, types of surgery, and antifibrinolytics, AWOF was associated with slightly greater amounts of ephedrine and phenylephrine but lesser amounts of epinephrine, norepinephrine, or vasopressin [Table 4]. There was no difference in the amounts of intravenous or CPB fluids [Table 4].
Table 2: Vasoactive medications

| Tool                        | Control 0 units (n=596) | 1 unit (n=482) | 2 units (n=1257) | 3 units (n=474) | P     |
|-----------------------------|-------------------------|----------------|------------------|----------------|-------|
|                            | n (%)                   | n (%)          | n (%)            | n (%)          |       |
| Ephedrine                  | 104 (17)                | 112<sup>a</sup> (23) | 341<sup>b</sup> (27) | 128<sup>a</sup> (27) | <0.001 |
| Epinephrine                | 96 (16)                 | 45<sup>a</sup> (9)  | 117<sup>a</sup> (9)  | 38<sup>a</sup> (8) | <0.001 |
| Norepinephrine             | 1 (0.2)                 | 0 (0)           | 3 (0.2)          | 0 (0)          | 0.530 |
| Phenylephrine              | 552 (93)                | 453 (94)        | 1194 (95)        | 464<sup>a</sup><sup>b</sup><sup>c</sup> (98) | 0.001 |
| Vasopressin                | 88 (15)                 | 75 (16)         | 147<sup>b</sup> (12) | 70 (15)        | 0.082 |
| Vasoactive bolus total dose|                        |                |                  |                |       |
| Ephedrine (mg)             | 0 (0, 0)                | 0<sup>a</sup> (0, 0) | 0<sup>a</sup><sup>b</sup> (0, 5) | 0<sup>b</sup><sup>c</sup> (0, 5) | <0.001 |
| Epinephrine (mcg)          | 0 (0, 0)                | 0<sup>a</sup> (0, 0) | 0<sup>a</sup><sup>b</sup> (0, 0) | 0<sup>b</sup><sup>c</sup> (0, 0) | <0.001 |
| Norepinephrine (mcg)       | 0 (0, 0)                | 0<sup>a</sup> (0, 0) | 0<sup>a</sup><sup>b</sup> (0, 0) | 0<sup>b</sup><sup>c</sup> (0, 0) | 0.530 |
| Phenylephrine (mcg)        | 900 (388, 1700)         | 1100<sup>a</sup> (500, 2100) | 1190<sup>b</sup><sup>c</sup> (550, 2000) | 1500<sup>b</sup><sup>c</sup> (900, 2300) | <0.001 |
| Vasopressin (units)        | 0 (0, 0)                | 0<sup>a</sup> (0, 0) | 0<sup>a</sup><sup>b</sup> (0, 0) | 0<sup>b</sup><sup>c</sup> (0, 0) | 0.094 |
| Vasoactive infusion dose   |                        |                |                  |                |       |
| Ephedrine (mg)             | 32 (10, 120)            | 20<sup>a</sup> (10, 40) | 20<sup>a</sup><sup>b</sup> (10, 50) | 19<sup>b</sup><sup>c</sup> (10, 24) | 0.011 |
| Norepinephrine (mcg)       | 196 (0, 694)            | 163<sup>a</sup> (0, 448) | 117<sup>b</sup><sup>c</sup> (0, 431) | 118<sup>b</sup><sup>c</sup> (0, 416) | 0.003 |
| Phenylephrine (mcg)        | 3.3 (0.6, 7.5)          | 4.3<sup>a</sup> (1.7, 7.7) | 4.3<sup>a</sup><sup>b</sup> (1.6, 7.7) | 5.0<sup>b</sup><sup>c</sup> (2.4, 8.9) | <0.001 |
| Vasopressin (units)        | 0 (0, 0)                | 0<sup>a</sup> (0, 0) | 0<sup>a</sup><sup>b</sup> (0, 0) | 0<sup>b</sup><sup>c</sup> (0, 0) | 0.001 |

A < 0.01, a < 0.05 compared to Control Group, B < 0.01, b < 0.05 compared to autologous blood removal without fluid replacement group with 1 unit removed, C < 0.01, c < 0.05 compared to autologous blood removal without fluid replacement group with 2 units removed. IQR = interquartile range.

Transfusions

Overall, 1322 (47%) of patients were transfused RBC intraoperatively and 1425 (51%) at any time. We found that there was a decrease in the proportion of patients given intraoperative RBC transfusions as the number of autologous units increased: 75% (0 units) to 48% (1 unit), 40% (2 units), and 30% (≥3 units), P < 0.001. We also found similar decreases in plasma and platelet transfusions from 53% to 19%, P < 0.001 and from 57% to 23%, P < .001, respectively, but not in cryoprecipitate [Table 3]. After we adjusted for other factors associated with RBC transfusion, patients with AWOF were less likely to be given RBC, plasma, and platelets and AWOF was associated with fewer units of RBC, plasma, and platelets transfused [Table 5]. However, the number of cryoprecipitate units transfused was decreased only for patients with three units removed. Any (intraoperative + postoperative) homologous transfusions were similarly decreased by AWOF [Tables 3 and 5].

Postoperatively, first ICU hematocrits were slightly lower in Control Group and AWOF = 1 compared to AWOF Groups 2 and 3: (Control) 27.5 ± 4.4% versus (Group 1) 27.1 ± 4.3%, versus (Group 2) 28.1 ± 4.0%, versus (Group 3) 28.3 ± 3.9%, respectively, P < .001. After adjusting for other factors, AWOF was associated with slightly lower or similar hematocrit levels on ICU arrival [B = -0.9 (-1.4,-0.4), P < .001; B = -0.3 (-0.8,0.1), P = 0.120; and B = -0.2 (-0.8,0.4) P = 0.480]. Platelet counts at ICU arrival were lower in the AWOF groups [Table 2] but after adjustment, only AWOF of three units was associated with lower counts (B = -20 (-27,-13), P < 0.001 [Table 4].

Other outcomes

AWOF patients with two or three units removed had slightly lower rates of KDIGO stage 1 or 3 AKI [Table 3]. However, after using logistic regression, AWOF was not associated with AKI [Table 5]. Reexplanation for hemorrhage did not differ among groups [Table 3].

Sensitivity analyses

When we repeated the regressions using actual intravenous and cardiopulmonary fluids instead of adjusting for the putative greater volume expansion attributed to albumin, we had similar results [Supplementary Tables 1 and 2]. In particular, AWOF was still associated with lower odds of transfusion and fewer units when transfused. Compared to Control Group, AWOF of 1, 2, or 3 units was associated with lower counts (B = -20 (-27,-13), P < 0.001 [Table 4].

Propensity score matching

When we used propensity scores to match patients with AWOF to Control patients, we had 488 well-matched patients.
Table 3: Transfusions and other outcomes

|                          | Control n=596 | Number of units of blood removed |          |
|--------------------------|---------------|----------------------------------|----------|
|                          | 0 units       | 1 unit n=482                     | 2 units n=1257 | 3 units n=474 |
|                          | 1376          | 1494                            | 1614      | 1734         |
|                          | n=1257        | n=1257                          | n=1257    | n=1257       |
|                          | %             | %                                | %         | %            |
|                          |               |                                  |           |              |
| Intraoperative transfusion|               |                                  |           |              |
| Blood units removed      |               |                                  |           |              |
| Red cells                | 449           | 75                               | 229       | 48           | 504       | 80         | 40         | 30         |
| Plasma                   | 313           | 53                               | 132       | 27           | 37         | 1         | 30         | 19         |
| Platelet                 | 341           | 57                               | 143       | 30           | 42         | 34        | 108       | 23         |
| Cryoprecipitate          | 82            | 14                               | 27        | 6            | 155        | 12        | 37         | 8          |
| Postoperative transfusion|               |                                  |           |              |
| Blood units removed      |               |                                  |           |              |
| Red cells                | 139           | 23                               | 68        | 14           | 110       | 9         | 33        | 7          |
| Plasma                   | 30            | 5                                | 8         | 2            | 26        | 2         | 5         | 1          |
| Platelets                | 39            | 7                                | 14        | 3            | 33        | 3         | 9         | 2          |
| Any transfusions         | 2             | 0.3                              | 0         | 0.2          | 0         | 0.2      | 0         | 0.399      |

|                          | Median | IQR  | Median | IQR  | Median | IQR  | Median | IQR  | P       |
|--------------------------|--------|------|--------|------|--------|------|--------|------|---------|
| Intraoperative transfusions|        |      |        |      |        |      |        |      |         |
| Red cells (units)         | 3      | (1, 6) | 0     | (0, 2) | 0     | (0, 2) | 0     | (0, 1) | <.001   |
| Plasma (units)            | 1      | (0, 4) | 0     | (0, 1) | 0     | (0, 2) | 0     | (0, 0) | <.001   |
| Platelets (units)         | 1      | (0, 4) | 0     | (0, 1) | 0     | (0, 2) | 0     | (0, 0) | <.001   |
| Cryoprecipitate (units)   | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0.009   |
| Postoperative transfusions|        |      |        |      |        |      |        |      |         |
| Red cells (units)         | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | <.001   |
| Plasma (units)            | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | <.001   |
| Platelets (units)         | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | <.001   |
| Cryoprecipitate (units)   | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0.400   |
| Any transfusions          | 3      | (1, 6) | 0     | (0, 2) | 0     | (0, 2) | 0     | (0, 1) | <.001   |
| Plasma (units)            | 1      | (0, 4) | 0     | (0, 1) | 0     | (0, 2) | 0     | (0, 0) | <.001   |
| Platelets (units)         | 1      | (0, 4) | 0     | (0, 1) | 0     | (0, 2) | 0     | (0, 0) | <.001   |
| Cryoprecipitate (units)   | 0      | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | 0     | (0, 0) | <.001   |
| Other Outcomes            |        |      |        |      |        |      |        |      |         |
| Mean                     | 7.32   | 0.09 | 7.34   | 0.06 | 7.33   | 0.06 | 7.32   | 0.05 | 0.744   |
| Standard deviation        | 3.6    | 2.8  | 3.6    | 2.8  | 3.6    | 2.8  | 3.6    | 2.8  | 0.410   |
| Minimum arterial pH       | 22.0   | 4.4  | 22.0   | 4.4  | 22.0   | 4.4  | 22.0   | 4.4  | 0.128   |
| Maximum lactic acid (mmol/L) | 12.6  | 4.4  | 12.6   | 4.4  | 12.6   | 4.4  | 12.6   | 4.4  | 0.001   |
| Minimum bicarbonate (mEq/L)   | 0.3    | 0.3  | 0.3    | 0.3  | 0.3    | 0.3  | 0.3    | 0.3  | 0.001   |
| First ICU hematocrit (%)   | 156    | 58   | 145    | 52   | 144    | 50   | 127    | 39   | <.001   |
| Reexploration             | 23     | 4    | 14     | 3    | 32     | 3    | 12     | 3    | 0.432   |
| KDIGO stage 1             | 165    | 28   | 141    | 29   | 301    | 24   | 107    | 23   | 0.097   |
| KDIGO stage 2             | 24     | 3    | 15     | 3    | 43     | 3    | 18     | 4    | 0.917   |
| KDIGO stage 3             | 39     | 7    | 16     | 3    | 25     | 2    | 8      | 2    | <.001   |

A < .01, a < .05 compared to Control Group, B < .01, b < .05 compared to autologous blood removal without fluid replacement group with 1 unit removed, C < .01, c < .05 compared to autologous blood removal without fluid replacement group with 2 units removed. Any transfusion is intraoperative + postoperative transfusion. KDIGO – Kidney Disease: Improving Global Outcomes. SD – standard deviation. IQR – interquartile range.

In these paired patients, AWOF patients were more likely to receive vasopressor boluses, more phenylephrine but less norepinephrine, and slightly more fluid adjusted for albumin dose [Supplementary Table 3]. In this paired analysis, AWOF patients were less likely to receive intraproductive homologous blood transfusions (75 vs. 53%, P < .001 for RBC; 53 vs. 34%, P < .001 for plasma; 57 vs. 39%, P < .001 for platelets), but had similar rates of cryoprecipitate [Supplementary Table 3]. These differences persisted through the postoperative period. Despite this higher transfusion amount, Control patients did not have higher postoperative hematocrits [Supplementary Table 3].

**DISCUSSION**

We found that we were successful at removing 1 – 3 units of blood for later transfusion with minimal, if any, increase in intravenous fluids and only small increases in vasopressor requirements. This amount of intraproductive blood collection was associated with fewer transfusions and was well tolerated with no increase in lactic acid,
Intraoperative transfusions

| Factor                        | 1 unit | 2 units | 3 units |
|-------------------------------|--------|---------|---------|
|                               | B      | 95% CI  | P       | B      | 95% CI  | P       | B      | 95% CI  | P       |
| Vasopressor boluses (#)       | 2      | (1, 3)  | 0.001  | 2      | (1, 3)  | <.0001 | 4      | (3, 6)  | <.0001 |
| Ephedrine dose (mg)           | 1      | (0, 2)  | 0.118  | 2      | (1, 3)  | <.0001 | 2      | (1, 4)  | <.0001 |
| Phenylephrine bolus dose (mcg)| 97     | (-117, 311) | 0.373 | 62     | (-109, 233) | 0.480 | 425    | (212, 639) | <.0001 |
| Phenylephrine total dose (mcg)| 340    | (-680, 1360) | 0.513 | 383    | (-432, 1999) | 0.357 | 1844   | (812, 2876) | <.0001 |
| Epinephrine total dose (mg)   | -116   | (-181, -52) | <.001 | -125   | (-176, -73) | <.0001 | -154   | (-219, -89) | <.0001 |
| Norepinephrine total dose (mg)| -145   | (-261, -28) | 0.015 | -238   | (-331, -145) | <.0001 | -254   | (-372, -136) | <.0001 |
| Vasopressin total dose (units)| -0.2   | (-1.1, 0.7) | 0.652 | -0.7   | (-1.4, 0.1) | 0.073 | -1.4   | (-2.4, -0.4) | 0.005  |
| CPB fluids adjusted (mL)     | 3      | (-71, 77) | 0.937 | 104    | (45, 164) | <.0001 | 182    | (106, 257) | <.0001 |
| Intravenous fluids adjusted (mL)| -38     | (-139, 64) | 0.470 | 89     | (8, 170)  | 0.032 | 101    | (-4, 205)  | 0.059  |
| Minimal arterial pH           | 0.01   | (0.001, 0.2) | 0.022 | 0.01   | (0.00, 0.02) | 0.005 | 0.01   | (0.00, 0.02) | 0.058  |
| Maximum lactate (mmol/L)      | -0.6   | (-0.8, -0.4) | <.0001 | -0.3   | (-0.5, -0.1) | <.0001 | -0.5   | (-0.7, -0.3) | <.0001 |
| Minimum bicarbonate (mEq/L)   | 0.2    | (-0.1, 0.5) | 0.298 | 0.5    | (0.2, 0.7)  | <.0001 | 0.6    | (0.3, 0.9)  | <.0001 |

Intraoperative transfusions

| Factor                        | 1 unit | 2 units | 3 units |
|-------------------------------|--------|---------|---------|
|                               | B      | 95% CI  | P       | B      | 95% CI  | P       | B      | 95% CI  | P       |
| Red cell (units)              | -2     | (-3, -1) | <.0001 | -2     | (-3, -2) | <.0001 | -4     | (-5, -3) | <.0001 |
| Plasma (units)                | -1     | (-2, -1) | <.0001 | -1     | (-2, -1) | <.0001 | -3     | (-3, -2) | <.0001 |
| Platelets (units)             | -1     | (-1, -0.3) | 0.002 | -1     | (-1, -0.4) | 0.002 | -2     | (-3, -2) | <.0001 |
| Cryoprecipitate (units)       | -0.1   | (-0.3, 0) | 0.163 | -0.1   | (-0.2, 0) | 0.202 | -0.5   | (-0.7, -0.3) | <.0001 |
| First postoperative hematocrit (%)| -0.9  | (-1.4, 0.4) | <.0001 | -0.3   | (-0.8, 0.1) | 0.120 | -0.2   | (-0.8, 0.4) | 0.480  |
| First ICU platelet count (1000/µL)| -4     | (-10, 1) | 0.139 | -4     | (-9, 1)  | 0.141 | -20    | (-26, -13) | <.0001 |

Any transfusions

| Factor                        | 1 unit | 2 units | 3 units |
|-------------------------------|--------|---------|---------|
|                               | B      | 95% CI  | P       | B      | 95% CI  | P       | B      | 95% CI  | P       |
| Red cell (units)              | -3     | (-4, -3) | <.0001 | -3     | (-4, -3) | <.0001 | -5     | (-6, -4) | <.0001 |
| Plasma (units)                | -2     | (-3, -1) | <.0001 | -2     | (-2, -1) | <.0001 | -4     | (-4, -3) | <.0001 |
| Platelets (units)             | -1     | (-2, -1) | <.0001 | -1     | (-2, -1) | <.0001 | -3     | (-3, -2) | <.0001 |
| Cryoprecipitate (units)       | -0.3   | (-0.4, 0.1) | 0.004 | -0.1   | (-0.3, 0) | 0.117 | -0.3   | (-0.5, -0.1) | 0.001  |

CPB – cardiopulmonary bypass. B – linear regression coefficient. Compared to no autologous blood removed, B is the change in the amount of the factor when autologous blood was removed and then transfused. 95% CI – 95% confidence interval

Importantly, we found that AWOF was not associated with AKI, which is similar to one study of ANH, but different than another ANH study, which found lower (28.2% v 24.1%, P < .001) rate of AKI in patients with autologous blood transfusions.[6,7] While transfusion in cardiac surgery has been associated with AKI,[21] unlike Goldberg et al’s study,[7] we did not find autologous blood to be associated with a lower AKI rate. Our study differs by removing blood without replacing the lost volume, which may contribute to a fall in cardiac output and renal blood flow. However, compared to ANH, it maintains hematocrit and thus may produce similar oxygen delivery.

We also found that despite fewer RBC transfusions, the change in hematocrit from postinduction to ICU was similar in the propensity matched groups. Our findings of fewer RBC, plasma, and platelet transfusions are similar to studies that used ANH.[6,8-11] Given the small numbers of patients who received cryoprecipitate, we may have been underpowered to find a benefit. Platelet count on ICU arrival was lower in the third unit AWOF group [Table 3]; but this was not associated with increased rate of reexploration for hemorrhage [Table 3].

AWOF was associated with a 33-36% lower odds ratio of receiving homologous blood transfusions per unit of blood removed [Table 5]. Our findings of decreased autologous transfusions in AWOF is similar to both prospective randomized and retrospective observational studies and one meta-analysis that found that ANH reduces transfusions.[6-8,10-11] Its similarity is obvious that larger amounts of autologous transfusions were associated with lesser transfusion rates. Our results differ from two studies that found no benefit from ANH.[12,13] While the volume of autologous blood removed in one study was relatively smaller (1 unit),[13] the volume in the other study was larger [1,099 ± 333 ml (range, 430–1900 ml)].[12] It is possible that large volume removal with fluid replacement leads to excessive hemodilution such that subsequent transfusion is necessary. Other studies of autologous transfusion did not provide information on vasopressors, making comparisons difficult.[22-24]

AWOF attempts to balance the benefits of autologous blood transfusion with the risks of hypovolemia. Larger volumes of autologous blood result in a higher...
hematocrit and may proportionally decrease platelet and plasma transfusions by providing fresh platelets and clotting factors postbypass when they are needed. However, larger volumes of autologous blood removal increase the risk of hypovolemia, need for vasopressors, and organ hypoperfusion and injury. Administration of intravenous fluids to maintain normovolemia (ANH) leads to hemodilution, anemia, and the potential for organ dysfunction. In particular, anemia on CBP is associated with AKI and mortality—probably from the decreased oxygen carrying capacity of the resultant anemic blood.[21,25] AWOF by minimizing hemodilution should lead to a higher oxygen carrying capacity, but its effects on oxygen delivery need further study.

Our study extends those findings to the use of AWOF and shows that AWOF is achievable and has no evidence of perfusion deficits as measured by acid–base balance or AKI. Future studies should compare AWOF to ANH, as AWOF should produce less hemodilution and may lead to fewer transfusions. Additionally, the lesser blood volume may contribute to decreased hemorrhage.[24]

There are several limitations to this study. First, this is a single center study and individual transfusion practices may not be generalizable to other institutions. Multi-center study is needed to confirm our finding. Second, as this was not a blinded study and there was no transfusion protocol, decisions to order homologous blood may have been based, at least in part, on the lack of autologous blood. This bias would create an apparent benefit to transfusion based, at least in part, on the lack of autologous blood.

In conclusion, we found that AWOF of 1-3 units for later autologous transfusion is associated with decreased homologous transfusions without acidosis or AKI.
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Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1. Linear regression showing the association between processes of care, intermediate outcomes and the number of autologous blood units removed to patients with no autologous blood removed (Control group). Regressions used the unadjusted intravenous fluids and cardiopulmonary bypass volume. Any transfusion is sum of intraoperative and postoperative. CPB – cardiopulmonary bypass. B – linear regression coefficient. Compared to no autologous blood removed, B is the change in the amount of the factor when autologous blood was removed and then transfused. 95% CI – 95% confidence interval.

| Factor                              | 1 unit |              | 2 units |              | 3 units |              |
|-------------------------------------|--------|--------------|---------|--------------|---------|--------------|
| Number of units of blood removed    |        |              |         |              |         |              |
| Factor                              | B      | 95% CI       | p-value | B            | 95% CI  | p-value      | B        | 95% CI       | p-value  |
| Vasopressor boluses (#)             | 1      | (0, 2)       | 0.017   | 2            | (1, 3)  | <0.001       | 4        | (3, 6)       | <0.001   |
| Ephedrine dose (mg)                 | 0      | (-1, 2)      | 0.492   | 2            | (1, 3)  | <0.001       | 2        | (0, 3)       | 0.036    |
| Phenylephrine bolus dose (mcg)      | 97     | (-117, 311)  | 0.373   | 62           | (-109, 233) | 0.480 | 425     | (212, 639)  | <0.001   |
| Phenylephrine total dose (mcg)      | 590    | (-422, 1602) | 0.253   | 408          | (-447, 1262) | 0.350 | 1453    | (274, 2632) | 0.016    |
| Epinephrine total dose (mcg)        | -97    | (-163, -33)  | 0.003   | -132         | (-187, -78) | <0.001 | -194    | (-270, -119) | <0.001   |
| Norepinephrine total dose (mcg)     | -71    | (-186, 44)   | 0.229   | -184         | (-281, -87) | 0.546 | -230    | (-364, -96)  | <0.001   |
| Vasopressin total dose (units)      | -0.2   | (-1.1, 0.6)  | 0.595   | -0.7         | (-1.4, 0.1) | 0.077 | -1.4     | (-2.4, -0.4) | 0.006    |
| CPB fluids (mL)                     | -75    | (-337, 187)  | 0.575   | -59          | (-280, 163) | 0.603 | 216     | (-89, 521)  | 0.116    |
| CPB fluids adjusted (mL)            | -124   | (-402, 154)  | 0.382   | -90          | (-325, 145) | 0.454 | 147     | (177, 471)  | 0.374    |
| Intravenous fluids (mL)             | -211   | (-492, 70)   | 0.141   | -117         | (-354, 121) | 0.336 | 69      | (-258, 397) | 0.678    |
| Intravenous fluids adjusted (mL)    | -274   | (-593, 45)   | 0.093   | -42          | (-312, 228) | 0.759 | 171     | (-201, 543) | 0.369    |
| Minimal arterial pH                 | 0.01   | (0.01, 0.2)  | 0.002   | 0.01         | (0.00, 0.01) | 0.084 | 0.017   | (0.00, 0.02) | 0.038    |
| Maximum lactate (mmol/L)            | -0.7   | (-0.9, -0.4) | <0.001  | -0.4         | (-0.6, -0.2) | <0.001 | -0.7     | (-0.9, -0.4) | <0.001   |
| Minimum bicarbonate (mEq/L)         | 0.2    | (-0.1, 0.5)  | 0.266   | 0.4          | (0.1, 0.6)  | 0.004 | 0.5      | (0.1, 0.9)  | 0.011    |
| Intraoperative transfusions         |        |              |         |              |         |              |
| Red cell (units)                    | -2     | (-3, -1)     | <0.001  | -2           | (-3, -2)  | <0.001       | -4       | (-5, -3)     | <0.001   |
| Plasma (units)                      | -1     | (-2, -1)     | <0.001  | -1           | (-2, -1)  | <0.001       | -3       | (-3, -2)     | <0.001   |
| Platelets (units)                   | -1     | (-1, -0.3)   | 0.002   | -1           | (-1, -0.4) | <0.001       | -2       | (-3, -2)     | <0.001   |
| Cryoprecipitate (units)             | -0.1   | (-0.3, 0)    | 0.163   | -0.1         | (-0.2, 0)  | 0.202 | -0.5     | (-0.7, -0.3) | <0.001   |
| First ICU hematocrit (%)            | -0.7   | (-1.3, -0.2) | 0.005   | -0.4         | (-0.8, 0.1) | 0.100 | -0.2     | (-0.8, 0.4)  | 0.217    |
| First ICU platelet count (1000/µL)  | -5     | (-10, 1)     | 0.115   | -4           | (-9, 1)   | 0.106 | -20      | (-27, -13)  | <0.001   |
| Any transfusions                    |        |              |         |              |         |              |
| Red cell (units)                    | -2     | (-3, -1)     | <0.001  | -3           | (-3, -2)  | <0.001       | -5       | (-6, -3)     | <0.001   |
| Plasma (units)                      | -1     | (-2, -1)     | <0.001  | -1           | (-2, -1)  | <0.001       | -3       | (-4, -3)     | <0.001   |
| Platelets (units)                   | -1     | (-1, -0.3)   | 0.001   | -1           | (-1, -0.5) | <0.001       | -3       | (-3, -2)     | <0.001   |
| Cryoprecipitate (units)             | -0.1   | (-0.3, 0)    | 0.108   | -0.1         | (-0.2, 0)  | 0.070 | -0.6     | (-0.8, -0.4) | <0.001   |
Supplementary Table 2. Adjusted odds ratio in patients with 1, 2, or 3 units of autologous blood removed compared to patients who had no autologous blood removed (Control group). Regressions used the unadjusted intravenous fluids and cardiopulmonary bypass volume. Any transfusion is sum of intraoperative and postoperative. KDIGO – Kidney disease improving global outcome, within the first 3 postoperative days. Undefined.

| Number of units of blood removed | 1 unit | 2 units | 3 units |
|----------------------------------|--------|---------|---------|
| **Factor**                       | Odds ratio 95% CI | p-value | Odds ratio 95% CI | p-value | Odds ratio 95% CI | p-value |
| Calcium administration           | 2.26 (0.61, 8.41) | 0.223   | 2.28 (0.88, 5.95) | 0.091   | undef (0, ∞)   | 0.986   |
| Any vasopressor infusion         | 1.69 (0.90, 3.15) | 0.101   | 1.62 (1.01, 2.59) | 0.044   | 1.87 (0.97, 3.61) | 0.061   |
| Ephedrine administration         | 1.14 (0.81, 1.60) | 0.461   | 1.73 (1.32, 2.26) | <0.001  | 1.90 (1.37, 2.64) | <0.001  |
| Intraoperative transfusion       |        |         |         |         |         |         |
| Red cell                         | 0.35 (0.25, 0.50) | <0.001  | 0.24 (0.17, 0.32) | <0.001  | 0.09 (0.06, 0.13) | <0.001  |
| Plasma                           | 0.50 (0.36, 0.70) | <0.001  | 0.37 (0.28, 0.48) | <0.001  | 0.09 (0.06, 0.13) | <0.001  |
| Platelet                         | 0.48 (0.35, 0.66) | 0.001   | 0.39 (0.29, 0.51) | <0.001  | 0.10 (0.07, 0.16) | <0.001  |
| Cryoprecipitate                  | 0.58 (0.34, 1.01) | 0.053   | 0.81 (0.56, 1.16) | 0.248   | 0.22 (0.13, 0.37) | <0.001  |
| **Any transfusions**             |        |         |         |         |         |         |
| Red cells (units)                | 0.41 (0.28, 0.60) | <0.001  | 0.25 (0.18, 0.34) | <0.001  | 0.09 (0.06, 0.15) | <0.001  |
| Plasma (units)                   | 0.48 (0.34, 0.67) | <0.001  | 0.36 (0.26, 0.48) | <0.001  | 0.08 (0.05, 0.12) | <0.001  |
| Platelets (units)                | 0.43 (0.31, 0.60) | <0.001  | 0.39 (0.29, 0.52) | <0.001  | 0.11 (0.07, 0.17) | <0.001  |
| Cryoprecipitate (units)          | 0.47 (0.26, 0.88) | 0.017   | 0.81 (0.53, 1.23) | 0.315   | 0.18 (0.09, 0.33) | <0.001  |
| KDIGO stage 1 or worse           | 1.15 (0.85, 1.55) | 0.378   | 0.98 (0.76, 1.27) | 0.888   | 0.91 (0.64, 1.28) | 0.572   |
| KDIGO stage 2 or worse           | 0.64 (0.33, 1.23) | 0.181   | 0.85 (0.51, 1.41) | 0.516   | 0.71 (0.34, 1.48) | 0.361   |
Supplementary Table 3. Propensity score matched no autologous blood removed with autologous blood removed patients with processes of care and outcomes. Any transfusion is intraoperative + postoperative transfusion. KDIGO – Kidney disease improving global outcome. CPB – cardiopulmonary bypass.

| Factor                                | No Autologous |         | Yes Autologous |         | p-value |
|---------------------------------------|---------------|---------|----------------|---------|---------|
|                                       | N = 488       | n       | %              | N = 488 | n       | %       |
| Received vasopressor infusion         | 455 93        | 476     | 98             | 0.023   |
| Received ephedrine                    | 86 18         | 128     | 26             | 0.002   |
| Intraoperative transfusion            |               |         |                |         |         |
| Red cells                             | 364 75        | 260     | 53             | <0.001  |
| Plasma                                | 259 53        | 166     | 34             | <0.001  |
| Platelets                             | 280 57        | 189     | 39             | <0.001  |
| Cryoprecipitate                       | 66 14         | 61      | 12             | 0.704   |
| Postoperative transfusion             |               |         |                |         |         |
| Red cells                             | 105 22        | 68      | 14             | 0.003   |
| Plasma                                | 23 5          | 14      | 3              | 0.180   |
| Platelets                             | 30 6          | 11      | 2              | 0.004   |
| Cryoprecipitate                       | 2 0.4         | 1       | 0.2            | 0.999   |
| Any transfusion                       |               |         |                |         |         |
| Red cells                             | 379 78        | 283     | 58             | <0.001  |
| Plasma                                | 261 53        | 167     | 34             | <0.001  |
| Platelets                             | 283 58        | 190     | 39             | <0.001  |
| Cryoprecipitate                       | 68 14         | 61      | 12             | 0.571   |
| KDIGO stage 1                         | 131 27        | 138     | 28             | 0.635   |
| KDIGO stage 2                         | 18 4          | 13      | 3              | 0.711   |
| KDIGO stage 3                         | 27 6          | 18      | 4              | 0.217   |
| Reexploration for hemorrhage          | 19 4          | 17      | 3              | 0.865   |
| Postinduction hematocrit (%)          |               |         |                |         |         |
| Vasopressor boluses (#)               | 9 (4, 14)     | 11 (6, 17) | <0.001 |
| Ephedrine (mg)                        | 0 (0, 0)      | 0 (0, 5) | <0.001 |
| Phenylephrine (mcg)                   | 4284 (1600, 8843) | 5634 (2732, 9184) | <0.001 |
| Epinephrine (mcg)                     | 0 (0, 0)      | 0 (0, 0) | 0.008  |
| Metric                               | Value 1                          | Value 2                          | p-value |
|--------------------------------------|----------------------------------|----------------------------------|---------|
| Norepinephrine (mcg)                 | 164 (0, 650)                     | 108 (0, 477)                     | 0.126   |
| Vasopressin (Units)                  | 0 (0, 0)                         | 0 (0, 0)                         | 0.094   |
| Intravenous fluids (mL)              | 1000 (1000, 1500)                | 1000 (1000, 1700)                | 0.099   |
| Intravenous fluids adjusted (mL)     | 1000 (1000, 2000)                | 1300 (1000, 2000)                | 0.003   |
| CPB volume (mL)                      | 1700 (988, 3100)                 | 2000 (1000, 3463)                | 0.033   |
| CPB volume adjusted (mL)             | 1800 (1000, 3500)                | 2100 (1000, 3525)                | 0.046   |
| Minimal arterial pH                  | 7.32 ± 0.09                      | 7.33 ± 0.06                      | 0.096   |
| Maximum lactic acid (mmol/L)         | 3.6 ± 2.5                        | 2.9 ± 1.8                        | <0.001  |
| Minimum bicarbonate (mEq/L)          | 22.1 ± 2.8                       | 22.0 ± 2.3                       | 0.780   |
| Nadir hematocrit (%)                 | 22.8 ± 4.2                       | 22.0 ± 4.0                       | 0.002   |
| First ICU hematocrit (%)             | 29.8 ± 4.5                       | 29.9 ± 4.0                       | 0.739   |
| First ICU platelet count (1000/µL)   | 154 ± 57                         | 144 ± 51                         | 0.004   |

Intraoperative transfusion

| Metric                               | Value 1                          | Value 2                          | p-value |
|--------------------------------------|----------------------------------|----------------------------------|---------|
| Red cells (units)                    | 3 (0, 6)                         | 1 (0, 3)                         | <0.001  |
| Plasma (units)                       | 1 (0, 4)                         | 0 (0, 2)                         | <0.001  |
| Platelets (units)                    | 1 (0, 4)                         | 0 (0, 2)                         | <0.001  |
| Cryoprecipitate (units)              | 0 (0, 0)                         | 0 (0, 0)                         | 0.551   |

Postoperative transfusion

| Metric                               | Value 1                          | Value 2                          | p-value |
|--------------------------------------|----------------------------------|----------------------------------|---------|
| Red cells (units)                    | 0 (0, 0)                         | 0 (0, 0)                         | 0.002   |
| Plasma (units)                       | 0 (0, 0)                         | 0 (0, 0)                         | 0.139   |
| Platelets (units)                    | 0 (0, 0)                         | 0 (0, 0)                         | 0.003   |
| Cryoprecipitate (units)              | 0 (0, 0)                         | 0 (0, 0)                         | 0.566   |

Any transfusion

| Metric                               | Value 1                          | Value 2                          | p-value |
|--------------------------------------|----------------------------------|----------------------------------|---------|
| Red cells (units)                    | 3 (1, 6)                         | 1 (0, 4)                         | <.001   |
| Plasma (units)                       | 1 (0, 4)                         | 0 (0, 2)                         | <.001   |
| Platelets (units)                    | 1 (0, 4)                         | 0 (0, 2)                         | <.001   |
| Cryoprecipitate (units)              | 0 (0, 0)                         | 0 (0, 0)                         | 0.452   |