Perfusion 2003; **18:** 115–121

Processing and transfusion of residual cardiopulmonary bypass volume: effects on haemostasis, complement activation, postoperative blood loss and transfusion volume

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The aim of this prospective randomized study was to compare the effects of the transfusion of unprocessed and cell saver-processed residual cardiopulmonary bypass (CPB) volume on haemostasis, complement activation, postoperative blood loss and transfusion requirements after elective cardiac surgery. Blood samples were taken at eight points in time, perioperatively. Haematological data, including haemoglobin, haematocrit and platelet counts as well as coagulation parameters, including activated partial thromboplastin time, prothrombin time, thrombin time, fibrinogen and the fibrinolytic parameter D-dimers, were measured from each blood sample. For the assessment of complement activation, the total complement CH50 was analysed. In addition, postoperative blood loss and transfusion requirements were measured during the first 24 hours, postoperatively.

The results of the study showed impaired haemostasis after the transfusion of both unprocessed and processed CPB volume. No significant differences were found between the groups in the measured coagulation parameters. Nor was a significant difference found in the complement concentration. However, in patients transfused with unprocessed CPB volume, a significantly ($p = 0.019$) higher amount of blood loss was found, postoperatively. In the same group of patients, the number of units of allogeneic erythrocyte concentrate suspension transfused was also significantly ($p = 0.023$) higher during the first 24 hours, postoperatively, compared to the patients transfused with processed CPB blood. The number of units of fresh frozen plasma and platelet suspension transfused was not significantly different between the groups. In conclusion, processing CPB volume in combination with processing peroperative blood loss may result in reducing the volume of transfusion needed of allogeneic blood products. *Perfusion* (2003) **18,** 115–121.

Introduction

One of the complications in cardiac surgery with cardiopulmonary bypass (CPB) is excessive intraoperative and postoperative blood loss. CPB involves extensive contact between blood and the artificial surfaces of the bypass circuit, thus, activating haemostasis, necessitating the use of systemic heparinization to prevent clotting in the extracorporeal circuit. The use of CPB also routinely results in a reduction in the platelet number and function, activation of fibrinolysis, haemodilution and induction of a systemic inflammatory response. Furthermore, duration of the perfusion, heparin dosage and the amount of cardiotomy suction during the operation are important factors that influence haemostasis.[1–5]

Blood loss is usually compensated by infusion of allogeneic blood products, which may cause a number of adverse effects, such as transfusion reactions and infection. For these reasons, it is important to reduce the need for transfusion of allogeneic blood products. There are different methods to achieve this, such as predonation, haemodilution, reduction of the priming volume of the CPB and postoperative transfusion of shed mediastinal fluid.[6,7]

Transfusion of the unprocessed residual volume of CPB is often applied after surgery. Little is known about the quality of unprocessed residual volume and the effects on haemostatis after its administration.[8] Flom-Halvorsen *et al.*[9] and Walpoth *et al.*[10]

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10.1191/0267659103pf647oa

showed that the infusion of residual unprocessed volume caused more blood loss and might increase inflammatory mediators. In the inflammatory cascade, activated components of the complement system contribute to all phases of the inflammatory response. In particular, the products that are generated after cleavage of C5, namely C5a and C5b-9, are potent inflammatory mediators with pleiotropic activities that include alteration of the blood vessel permeability and tone, leukocyte chemotaxis and activation of multiple inflammatory cell types.[11]

To decrease the adverse effects caused by the infusion of unprocessed residual volume, processing of this volume using a cell saver device is an alternative.[12,13] This method results in a product with an haematocrit value of 55–60% and free of unbound heparin. However, a disadvantage is loss of plasma proteins, platelets and coagulation factors. According to the literature, the cell saver procedure does not enhance complement activation, but significantly reduces the concentrations of the products of the complement system.[14,15]

This study was designed to investigate whether the transfusion of processed residual CPB volume improves postoperative haemostasis, decreases the concentration of complement activation products, decreases postoperative blood loss and reduces the transfusion requirement.

Material and methods

Patients

Forty patients undergoing elective coronary bypass graft procedures and/or cardiac valve operations were prospectively enrolled in this study (Tables 1 and 2). Informed consent was obtained from all patients according to the regulations of the hospital medical ethical committee. Patients were randomized into two groups.

Patients in Group 1 were transfused with unprocessed residual volume obtained from the extracorporeal circuit.

Table 1 Patient characteristics

	Group 1	*Group 2*	*p value*
Patient (*n*)	20	20	ns
Gender (m/f)	13m-7f	11m-9f	ns
Age (years)	65±10	64±14	ns
Body surface[1] (m^2)	1.87±0.19	1.88±0.19	ns
Bypass time (min)	146±54	161±46	ns
Crossclamp (min)	95±37	84±31	ns

Data are expressed as mean values and the standard error of the mean (SEM); *n*, number; m, male; f, female; ns, not significant.
[1] Body surface according to Dubois.

Table 2 Surgical interventions

	Group 1	*Group 2*	*p value*
AVR(±CABG)	5	4	ns
MVR/MPL(±CABG)	2	7	ns
AVR/MPL	1	0	ns
CABG	12	9	ns

CABG, coronary artery bypass grafting; AVR, aortic valve replacement/repair; MVR, mitral valve replacement/repair; MPL, mitral valve ring/patch; ns, not significant.

Patients in Group 2 were transfused with processed [with a blood cell saver device (Haemolite 2plus, Haemonetics Corp., Braintree, MA)] residual CPB volume.

Anaesthesia

Anaesthesia was standardized.

Premedication consisted of dormicum, 0.3 mg/kg. Induction of anaesthesia was achieved using sufentanyl (0.5–1 mg/kg), dormicum (0.2 mg/kg) and pavulon (0.1 mg/kg). All patients received dexamethasone (1.0 mg/kg).

Cardiopulmonary bypass and transfusion of the CPB residual volume

All patients were operated with CPB and cardioplegic arrest. Arterial cannulation was achieved in the aorta ascendens and venous cannulation via the right atrium or in the vena cavae, superior and inferior. A left ventricular drain or aortic root cannula was used for left ventricular venting. Myocardial preservation was achieved with antegrade cardioplegia (St Thomas' Hospital Solution, 4°C) delivered by gravity at 10–15 mL/kg body weight after applying of the aortic crossclamp. As a topical cooling, NaCl 0.9% at 4°C was used.

The CPB circuit consisted of a Cobe CML Duo flat-sheet oxygenator (Cobe Cardiovascular Inc., Arvada, CO) with an integrated heat exchanger, a venous/cardiotomy reservoir (Avecor, Medtronics Cardiopulmonary, Engelwood, CO) with filter, an arterial blood filter (Avecor Affinity, Medtronics Cardiopulmonary, Engelwood, CO) and a custom made uncoated PVC tubing pack (Heart Medica Europe, Best, The Netherlands) with silicone roller-pump tubing.

The circuit was primed with 1200–1400 mL Gelofusin (Braun Medical, Melsungen, Germany), 200 mL mannitol 20% (Baxter, Uden, The Netherlands), 100 mL human albumin (CeAlb, CLB, Amsterdam, The Netherlands), 25–30 mL $NaHCO_3$ 8.4% (Fresenius, Den Bosch, The Netherlands) and 4.2 IU heparin (Leo Pharmaceutical Products, Weesp, The Netherlands) per mL priming volume. Before cannulation, the patients were heparinized

with 300 IU heparin/kg body weight. Activated clotting time was measured by a Hemotec kaolin cartridge (Hemotec ACTII, Medtronic Inc., Anna-heim, CA) and was maintained above 480 seconds during the procedure.

Patients were systemically cooled to a nasophyaryngeal temperature between 28–32°C and weaned from CPB when the nasopharyngeal temperature was higher than 36°C and the rectal temperature reached 34°C. Blood flow rate was between 1.8 and 2.4 L/min/m^2 while maintaining the blood pressure between 40 and 80 mmHg and the on line monitoring venous saturation > 60%. Blood from the operative field was aspirated by vacuum-controlled cardiotomy suction (maximum, −60 mmHg). After the CPB, heparin was neutralized with protamine chloride at a dose of 4 mg/kg body weight. The CPB residual volume was then collected into the retransfusion bag (Cobe Cardiovascular Inc., Arvada, CO) – Group 1, or processed by the blood cell saver device – Group 2. The cell saver device was not used intraoperatively to salvage shed blood in either group. The transfusion of unprocessed as well as processed residual volume was done directly post-CPB in the operating room (OR) or during the first hours in the intensive care unit (ICU), according to the volume requirements of the patient. Because the unprocessed residual volume contained some amount of heparin, immediately after transfusion of it, the patients received extra protamine chloride calculated at a dose of 5 mg protamine per 100 mL transfused volume.

Allogeneic erythrocyte concentrate (EC) was administered in both groups when the patient's haemoglobin concentration measured lower than 5 mmol/L and/or the haematocrit was lower than 25% of the platelet suspension. Transfusion of fresh frozen plasma (FFP) was performed in cases of a fibrinogen concentration lower than 1.5 g/L and platelet suspension (PS) was used when the platelet count fell below 100×10^9/L.

Blood sampling

Venous blood samples were obtained one day preoperatively (T1), after induction of anaesthesia (T2), at 5 min before termination of CPB (T3), 10 min after administration of protamine chloride (T4) and at 2 hours (T5), 6 hours (T6), 18 hours (T7) and 24 hours (T8), postoperatively.

Study parameters

The following parameters were measured (see Table 3). The haemoglobin concentration (reference value 7.5–10.5 mmol/L), haematocrit (reference value 36–50%) and platelet count (reference value 130–330*10^9/L) were measured as haematological parameters. Furthermore, for coagulation measurements, the activated partial thromboplastin time (APTT, reference value 24–34 seconds), prothrombin time (PT, reference value 9.3–12.3 seconds) and thrombin time (TT, reference value 16–23 seconds) were performed. In addition, the fibrinogen concentration (reference value 1.5–3.6 g/L) as the fourth marker for the coagulation and D-dimers (reference value < 0.25 mg/L), as a parameter for the fibrinolysis were analysed. Finally, the total complement (CH-50 reference value 68–133%), as a parameter for the complement activation, was measured.

The blood loss and transfusion volume of each patient were measured during the first postoperative 24 hours.

Table 3 Scheme laboratory measurements

Sample	*HP*	*CP*	*FP*	*CAP*
T1	√	√	√	nt
T2	√	nt	√	√
T3	√	nt	√	√
T4	√	√	√	√
T5	√	√	√	√
T6	√	√	√	√
T7	√	√	√	√
T8	√	√	√	√

√, measurements; nt, not tested.
HP, haematological parameters: haemoglobin, haematocrit, platelets; CP, coagulation pararmeters: activated partial thromboplastin time, prothrombin time, thrombin time, fibrinogen; FP, fibrinolysis parameter: D-dimers; CAP, complement activation parameter: CH-50.

Data analysis

All values are expressed as mean ± standard error of the mean (SEM). Statistical calculations were performed using the computer program SPSS 9.0 (Scheffe procedure, Chicago, IL) using the one-way analysis of variance (ANOVA). p values less than 0.05 were considered statistically significant.

Results

Haematological parameters

At all measured points in time, the haemoglobin concentration, the haematocrit and the platelet numbers were decreased after induction of anaesthesia and further declined during CPB due to haemodulition. As time progressed, these values increased to reference values. The data showed no significant difference in haemoglobin concentration and haematocrit between Groups 1 and 2 (Table 3).

However, the platelet numbers were significantly decreased in sample T4 ($p = 0.046$) and sample T5 ($p = 0.011$) in Group 2 compared to Group 1 (Table 4).

Coagulation parameters

The measured coagulation profiles showed prolonged APTT and PT in both groups after the administration of protamine chloride (T4) in comparison with the preoperative measurement (T1). In the postoperative phase, this prolongation decreased to reference values at T8. At all points in time, TT measurements stayed within the reference values in both groups. The fibrinogen concentration declined by means of haemodilution at T2 and T3. Twenty-four hours postoperatively, fibrinogen concentrations were back to reference values in both groups.

There were no significant differences found of the measured coagulation parameters between Groups 1 and 2 (Tables 5 and 6).

Fibrinolysis

Hyperfibrinolysis, indicated by measurements of the concentration D-dimers, was found in both groups. However, no significant differences between the groups were found (Table 6).

Complement activation

CH-50 concentrations of all samples were decreased in both groups. Using the sample after induction of anaesthesia (T2) as a baseline, we saw the CH-50 concentration decline due to haemodilution after the onset of perfusion. The concentration slowly increased to reference values in both groups at 24 hours postoperatively. No significant differences were measured between the two groups (Table 7).

Postoperative blood loss

Blood loss was divided into blood loss postperfusion in the OR and the 24-hour postoperative blood loss during the ICU period (Table 8). During the postperfusion period in the OR, no significant difference was found while, during the ICU period, Group 1 blood loss was significantly higher than in Group 2.

Transfusion volume

Patients from Group 1 received unprocessed CPB residual volume (1312 ± 531 mL) with a mean hae-

Table 4 Haematological parameters

Sample	*Haemoglobin (mmol/L)*			*Haematocrit (%)*			*Platelets (10^9/L)*		
	Group 1	*Group 2*	*p value*	*Group 1*	*Group 2*	*p value*	*Group 1*	*Group 2*	*p value*
T1	8.2 ± 0.9	8.1 ± 0.6	ns	39 ± 4	39 ± 2	ns	271 ± 84	241 ± 50	ns
T2	6.6 ± 1.1	6.8 ± 0.8	ns	31 ± 5	32 ± 4	ns	200 ± 58	189 ± 44	ns
T3	4.7 ± 0.6	4.6 ± 0.5	ns	22 ± 3	22 ± 2	ns	150 ± 42	140 ± 35	ns
T4	4.7 ± 0.4	4.5 ± 0.6	ns	22 ± 2	21 ± 2	ns	123 ± 46	101 ± 37	0.046
T5	5.7 ± 0.5	6.1 ± 0.9	ns	26 ± 2	28 ± 4	ns	144 ± 38	120 ± 30	0.023
T6	6.3 ± 0.5	6.4 ± 0.7	ns	29 ± 3	30 ± 3	ns	145 ± 37	126 ± 35	ns
T7	6.8 ± 0.6	6.8 ± 0.7	ns	31 ± 3	32 ± 3	ns	145 ± 43	140 ± 47	ns
T8	7.1 ± 0.5	6.8 ± 0.5	ns	33 ± 2	32 ± 2	ns	153 ± 48	141 ± 44	ns

Data are expressed as mean values ± SEM; ns, not significant. Reference values: haemoglobin: 7.5–10.5 mmol/L; haematocrit: 36–50%; platelet count: 130–330 10^9/L. No differences between Groups 1 and 2 except for the platelet numbers in samples T4 and T5.

Table 5 Coagulation profiles

Sample	*APTT (seconds)*			*PT (seconds)*			*TT (seconds)*		
	Group 1	*Group 2*	*p value*	*Group 1*	*Group 2*	*p value*	*Group 1*	*Group 2*	*p value*
T1	28 ± 4	29 ± 6	ns	12 ± 4	12 ± 3	ns	22 ± 2	21 ± 3	ns
T4	39 ± 8	38 ± 5	ns	16 ± 4	17 ± 2	ns	18 ± 2	18 ± 2	ns
T5	34 ± 5	33 ± 5	ns	15 ± 1	15 ± 2	ns	17 ± 2	18 ± 3	ns
T6	32 ± 5	30 ± 5	ns	14 ± 1	14 ± 2	ns	18 ± 2	17 ± 2	ns
T7	30 ± 4	29 ± 4	ns	12 ± 1	12 ± 2	ns	17 ± 1	18 ± 4	ns
T8	28 ± 3	28 ± 4	ns	12 ± 1	12 ± 1	ns	17 ± 2	16 ± 2	ns

Data are expressed as mean values ± SEM; ns, not significant; APTT, activated partial thromboplastin time(reference value: 24–34 seconds); PT: prothrombin time (reference value: 9.3–12.3 seconds), TT: thrombin time (reference value: 16–23 seconds). No differences between Groups 1 and 2 for APTT, PT and TT.

Table 6 Fibrinogen and D-dimers concentration

Samples	*Fibrinogen (g/L)*			*D-dimers (mg/L)*		
	Group 1	*Group 2*	*p value*	*Group 1*	*Group 2*	*p value*
T1	3.5±0.6	3.6±0.7	ns	0.3±0.2	0.5±0.7	ns
T2	2.7±0.6	2.9±0.6	ns	0.3±0.4	0.3±0.4	ns
T3	1.5±0.3	1.7±0.4	ns	1.4±1.0	1.4±0.7	ns
T4	1.5±0.3	1.7±0.5	ns	1.7±1.0	1.7±1.0	ns
T5	1.8±0.4	1.8±0.5	ns	1.4±0.8	1.4±0.8	ns
T6	1.8±0.5	1.9±0.6	ns	0.9±0.7	1.2±0.8	ns
T7	2.5±0.4	2.6±0.5	ns	1.1±0.6	1.4±1.2	ns
T8	2.7±0.7	2.9±0.5	ns	1.3±0.8	1.5±1.6	ns

Data are expressed as mean values±SEM; ns, not significant; fibrinogen reference value: 1.5–3.6 g/L; D-dimers: reference value < 0.25 mg. No significant differences between Groups 1 and 2 for fibrinogen and D-dimers.

Table 7 CH-50 concentration

Sample	*CH-50 concentration (%)*		
	Group 1	*Group 2*	*p value*
T2	83±12	76±19	ns
T3	41±10	48±15	ns
T4	38±10	42±13	ns
T5	47±10	42±16	ns
T6	46±13	46±18	ns
T7	54±12	56±21	ns
T8	69±12	61±22	ns

Data are expressed as mean values±SEM; ns, not significant; CH-50 reference value: 68–133%. No significant differences between Groups 1 and 2 for CH-50.

matocrit of 22%. In Group 2, processed CPB residual volume was administered (490±201 mL) with a mean haematocrit of 59%.

Table 9 shows the volume transfused in the OR and the ICU. The mean amount of units of allogeneic EC administered in the OR was not different between Groups 1 and 2. However, in the ICU period, a significant ($p = 0.023$) difference was seen between the groups. The total amount of allogeneic EC administered was significantly different ($p = 0.046$) as well.

The number of units of fresh frozen plasma (FFP) and units of platelet suspension (PS) were not significantly different between the groups.

In both groups, the same volume replacement therapies were used. The patients in Group 1 received 6.6 (±2.8) and in Group 2, 5.7 (±2.6) units of gelofusin. The number of units of gelofusin were not significantly different between the groups ($p = 0.28$).

Table 8 Blood loss (ml) after perfusion

	Group 1	*Group 2*	*p value*
OR	558±603	421±403	ns
ICU	859±382	605±265	0.019

Data are expressed as mean±SEM; ns, not significant; OR, operating room; ICU, intensive care unit.

Discussion

The most important findings of this study could be listed as followed: 1) transfusion of processed residual volume from the CPB circuit did not improve postoperative haemostasis, 2) transfusion of processed residual volume did not result in a reduction of the concentration of complement activation products and 3) transfusion of processed residual volume did result in a reduction of blood loss and a reduction of the total number of units of allogeneic EC during the first 24 hours after the operation.

Table 9 Allogeneic blood products (units)

	Group 1	*Group 2*	*p value*
EC			
OR	0.6±0.8	0.9±1.0	ns
ICU	2.5±0.7	1.6±1.4	0.023
Total	3.2±1.1	2.4±1.3	0.046
FFP			
OR	0.8±1.0	1.0±0.9	ns
ICU	0.7±1.5	0.5±0.8	ns
Total	1.3±1.7	1.5±1.3	ns
PS			
OR	1/20	5/20	ns
ICU	2/20	1/20	ns
Total	3/20	6/20	ns

Data are expressed as mean±SEM except for PS, amount (n) out of total patients; ns, not significant; EC, erythrocyte concentrate suspension (unit); FFP, fresh frozen plasma (unit); PS, 5 donor platelet suspensions (unit).

This study showed no significant differences in concentrations of haemoglobin and haematocrit in either group at the measured points in time. The number of platelets was significantly lower in Group 2 compared with Group 1 at 2 and 6 hours after the operation procedure. An explanation for this temporary decrease was the transfusion of processed platelet-depleted residual CPB blood. Therefore, more patients in Group 2 (6 of 20) were administered with five donor platelet suspensions compared with Group 1 (3 of 20).

Considering the coagulation profiles, there was an impaired haemostasis balance in both groups. However, the values of coagulation parameters were not significantly different between the groups. Postoperative blood loss was decreased in Group 2 during the ICU period, resulting in a reduction of transfused volume.

Furthermore, transfusion of allogeneic blood products in the postoperative phase generally shaded the effects of transfusion of residual volume. The phenomenon of higher blood loss in the ICU period in Group 1 possibly can be explained by the effects of erythrocyte cell injury and high free haemoglobin.[16] Hornick *et al.*[17] suggested that the erythrocyte membrane could be attacked by the membrane attack complex (MAC), triggered by the activation of complement. In addition, erythrocyte deformability leads to reduced tissue flow by alteration of the rheologic properties of the blood. This, in turn, leads to reductions in tissue metabolism and oxygenation. It may also contribute to postbypass bleeding. Thus, by processing the residual volume, the deformed erythrocytes were eliminated and could lead to a reduction of the blood loss in the postoperative period.

In the literature, increased postoperative blood loss is often associated with insufficient reversal of the heparin. In this study, more protamine chloride was given in Group 1 to compensate for the presence of heparin in the reinfused blood. To exclude the heparin effect, we frequently perform heparin assessment. These tests were carried out using the Hepcon Management System (Medtronic). However, no differences in heparin concentrations in the patient blood, in either group, were found.

Also in the literature, the influence of activated complement products in relation to residual volume obtained from CPB remains unclear. The group of Arnestad[18] showed that transfusion of collected shed blood with elevated concentration of complement activation products did not lead to increased systemic concentrations of complement activation products. Bengtsson *et al.*[16] showed a reduction of the concentration of complement activation products in the processed residual volume from the CPB circuit. In this study, comparable concentrations of CH-50 complex were found in both groups. Therefore, neither the unprocessed nor the processed volume influenced the systemic concentration of complement activation products.

Furthermore, significantly more units of EC were used in the ICU period in Group 1 compared to Group 2. This can be easily accounted for by the higher haematocrit (55–60%) content in the processed residual volume. The saving of the expense of one unit of allogeneic EC counterbalances the cost of a cell saver disposable set. Therefore, routine usage of the cell saver device to process peroperative blood loss could reduce costs as well as further reduce the amount of allogeneic units of EC.

Acknowledgements

The authors would like to thank Nadine Rohoman for critical reading and correction of the manuscript.

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