

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2007;116:I-89-I-97

DOI: 10.1161/CIRCULATIONAHA.106.678987

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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The Cardiotomy Trial

A Randomized, Double-Blind Study to Assess the Effect of Processing of Shed Blood During Cardiopulmonary Bypass on Transfusion and Neurocognitive Function

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Background—Reinfusion of unprocessed cardiotomy blood during cardiac surgery can introduce particulate material into the cardiopulmonary bypass circuit, which may contribute to postoperative cognitive dysfunction. On the other hand, processing of this blood by centrifugation and filtration removes coagulation factors and may potentially contribute to coagulopathy. We sought to evaluate the effects of cardiotomy blood processing on blood product use and neurocognitive functioning after cardiac surgery.

Methods and Results—Patients undergoing coronary and/or aortic valve surgery using cardiopulmonary bypass were randomized to receive unprocessed blood (control, n=134) or cardiotomy blood that had been processed by centrifugal washing and lipid filtration (treatment, n=132). Patients and treating physicians were blinded to treatment assignment. A strict transfusion protocol was followed. Blood transfusion data were analyzed using Poisson regression models. The treatment group received more intraoperative red blood cell transfusions (0.23 ± 0.69 U versus 0.08 ± 0.34 U, $P=0.004$). Both red blood cell and nonred blood cell blood product use was greater in the treatment group and postoperative bleeding was greater in the treatment group. Patients were monitored intraoperatively by transcranial Doppler and they underwent neuropsychometric testing before surgery and at 5 days and 3 months after surgery. There was no difference in the incidence of postoperative cognitive dysfunction in the 2 groups (relative risk: 1.16, 95% CI: 0.86 to 1.57 at 5 days postoperatively; relative risk: 1.05, 95% CI: 0.58 to 1.90 at 3 months). There was no difference in the quality of life nor was there a difference in the number of emboli detected in the 2 groups.

Conclusions—Contrary to expectations, processing of cardiotomy blood before reinfusion results in greater blood product use with greater postoperative bleeding in patients undergoing cardiac surgery. There is no clinical evidence of any neurologic benefit with this approach in terms of postoperative cognitive function. (*Circulation*. 2007;116[suppl I]: I-89–I-97.)

Key Words: nervous system ■ cardiopulmonary bypass ■ trials ■ hemorrhage ■ surgery

Diffuse brain injury is a serious and debilitating complication of cardiac surgery. Most investigators believe that this damage is a major contributor to the disorder of subtle intellectual decline referred to as postoperative cognitive dysfunction (POCD). This syndrome is relatively common because it may be seen in 35% to 75% of patients early postoperatively and in 11% to 40% 3 to 6 months after surgery.^{1–3} Furthermore, investigators have demonstrated that even if the early postoperative changes disappeared, affected individuals were more likely to show early dementia 5 years later.^{4–6}

Cardiopulmonary bypass (CPB) has been implicated as the most important contributor to cerebral injury related to cardiac surgery because the severity of POCD is greater after

cardiac surgery with CPB as compared with major noncardiac surgery.^{1,7–11} There are several injurious mechanisms directly related to CPB that may be causative of this problem^{1,7}; however, it has been proposed that microembolization, in particular from readministration of cardiotomy blood, may be the key element to this damage.^{12,13} Cardiotomy blood consists of the volume that collects in the pericardial cavity during CPB, which is generally aspirated and readministered into the venous reservoir of the pump. This blood is contaminated by cellular debris and fat particles that resemble the characteristic lipid-staining neuropathologic findings after CPB referred to as small capillary and arteriolar dilations.^{14–16} Animal models of CPB have also confirmed the relationship of cardiotomy blood readministration to the

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Presented at the American Heart Association Scientific Sessions, Chicago, Ill, November 12–15, 2006.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.106.678987

density of small capillary and arteriolar dilatations at autopsy.¹⁷

Because the quantity of cardiomy blood collected during CPB may be considerable,^{18,19} routinely discarding this blood in an effort to prevent microembolization may result in increased blood product requirements. As an alternative, up to 40% of cardiac teams regularly process cardiomy blood with centrifugal washing.²⁰ This technique involves centrifugation of the sterilely collected blood to separate the plasma components and debris from the heavier cellular elements. The plasma is siphoned from the blood and the cells are washed with isotonic saline. The final concentrated product may be collected and reinfused as required. This cleaning may be further enhanced by filtration using devices comprising either micropore (nylon screen) or 3-dimensional mesh (Dacron wool) to entrap blood particles, including fat and leukocytes.²¹ The combination of these 2 technologies in series represent the most effective means available to remove both soluble profibrinolytic material as well as lipid and large cell aggregates. On the other hand, the disposables required for these steps incur added expense, and there is potential for the loss of large volumes of plasma proteins, which may further compromise hemostatic integrity after CPB.

There are no well-designed clinical trials measuring relevant clinical outcomes that have addressed the question of the best management for cardiomy blood. Furthermore, we have documented large practice variations among cardiac surgical centers with regard to this issue.²⁰ To balance our understanding of a potential neuroprotective advantage of cardiomy blood processing, we sought to address the impact of this strategy on bleeding and transfusion rates and neurocognitive function in patients undergoing cardiac surgery.

Materials and Methods

Participants

The study protocol was approved by the Human Research Ethics Board of the University of Ottawa Heart Institute and written informed consent was obtained from all patients. Patients undergoing isolated, nonemergent coronary artery bypass at the University of Ottawa Heart Institute were recruited. Eight patients in each group were recruited who were undergoing aortic valve replacement, but they were excluded from the neuropsychological testing. Patients had to be fluent in English or French with no impediment to completing neuropsychological testing. Patients were screened with the Modified Mini-Mental State examination with a minimum cutoff of 24 out of 30 for recruitment. Patients with known neurologic deficits, preoperative coagulopathy, bleeding diathesis, or thrombocytopenia ($<140\,000/\mu\text{L}$) as well as those with renal (creatinine $>2\times$ normal) or hepatic insufficiency (elevated liver function tests, elevated baseline international normalized ratio) were excluded.

Interventions

Intraoperative Protocol

A narcotic-based anesthetic was used. The initial study protocol did not include the administration of antifibrinolytic agents; however, in response to a change in institutional practice, tranexamic acid (1-g bolus after induction and a 2.0-mg/kg/h intraoperative infusion) was administered to all study patients after June 2002 (n=224).

After sternotomy and conduit preparation, patients were heparinized to achieve an activated clotting time >400 seconds. CPB was conducted using a roller pump, a membrane oxygenator (COBE

CML Duo; COBE Cardiovascular Inc, Arvada, Colo), a 43- μm arterial filter (COBE Sentry with PrimeGuard), a closed venous reservoir bag, an ascending aortic cannula, and a 2-stage venous cannula return. The circuit was primed with 1300 mL of Ringer's lactate. Bypass flows were maintained at 2.4 to 3.2 L/m²/min. The heart was arrested using antegrade cold blood or crystalloid cardioplegia and topical cooling was used at the discretion of the surgeon. During cardiac anoxia, the body temperature was reduced to a systemic temperature of 34°C and at the completion of the procedure, patients were rewarmed taking care to never exceed 37°C (nasopharyngeal).

Group Interventions

During CPB in the control group, suctioned blood was collected in the cardiomy reservoir and transferred directly to the oxygenator after passage through the integrated cardiomy filter (40 μm). In the treatment group, cardiomy blood was diverted into the cell saver for centrifugal washing and then readministered into the pump after passage through a leukoreduction filter used to augment fat globule and leukocyte removal (Pall LeukoGuard RS Filter; Pall Biomedical Products Company, East Hills, NY).

Management of Postoperative Bleeding and Blood

Product Use

Patients received transfusions during CPB if the hematocrit was $<20\%$ and after CPB and postoperatively if the hematocrit was $<21\%$. Transfusions were given when the hematocrit was higher than this level if there was suspected inadequate oxygen delivery (eg, presence of a base deficit >5 mmol/L or a cardiac index <2.0 L/min/m²) or active bleeding. In both groups, all scavenged blood from the mediastinum from the time of administration of protamine up to 4 hours postoperatively was processed by centrifugal washing (BRAT; COBE Cardiovascular Inc) if the volume exceeded 1 L. After 4 hours, all subsequent shed blood was discarded. Patients underwent reexploration if bleeding was >500 mL in 1 hour or >1000 mL over 4 hours.

For patients bleeding between 100 and 250 mL/hr for 4 hours, blood products were given after heparin rebound had been ruled out using the following protocol:

1. Platelets in aliquots of 5 U if the platelet count is $<60\,000/\text{L}$ or if there was suspicion of platelet dysfunction (eg, long CPB run);
2. Fresh-frozen plasma (15 mL/kg) if the international normalized ratio was >1.8 ; or
3. Cryoprecipitate (0.25 U/kg) if the fibrinogen level was <1.0 g/L.

Tests of Coagulation

Coagulation profiles, including hemoglobin, platelets, partial thromboplastin time, thrombin time, international normalized ratio, and fibrinogen, levels were measured in all patients preoperatively, during anesthetic induction, 15 minutes after protamine administration, and 2, 4, and 12 hours after separation from CPB.

Neuropsychometric Testing:

The core tests used in this trial have been recommended by a consensus conference on assessment of neurobehavioral outcomes after cardiac surgery.²² The tests were divided into 4 domains using factor analysis as described by Newman et al²³:

1. Psychomotor speed and dexterity were measured by Trails A and B (maximum score 300 seconds), grooved pegboard (dominant hand, maximum score 300 seconds), and the Symbol Digit Modalities Test (oral administration).²³
2. Verbal Memory was assessed using the Rey auditory verbal learning test (RAVLT).
3. Attention span was evaluated with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span.
4. Executive Function was assessed with a verbal fluency test (including letters [FAS test] and categories [animal naming]).

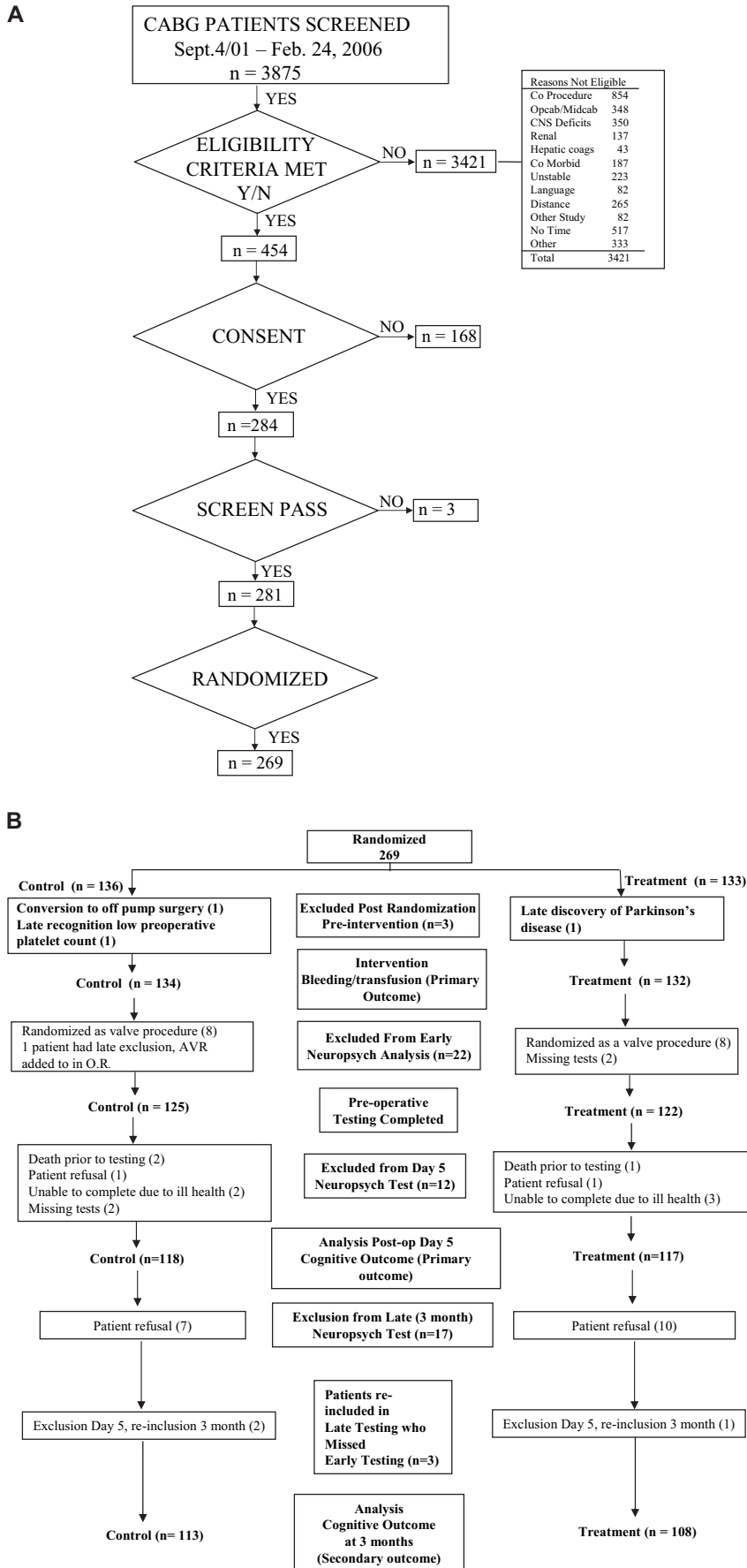


Figure 1. A, Patient screening and enrollment up to randomization. B, Patient flow postrandomization.

TABLE 1. Preoperative Data*

	Control (N=134)	Treatment (N=132)
Age, years	58.7±9.3	59.1±9.6
Male sex	121 (90)	117 (89)
Left ventricular ejection fraction <35%	58 (43)	55 (42)
CCS		
1	16 (12)	13 (10)
2	39 (29)	42 (32)
3	59 (44)	56 (42)
4	20 (15)	21 (16)
Left main disease	38 (28)	37 (28)
No. of diseased vessels		
0	2 (2)	2 (2)
1	3 (2)	3 (2)
2	27 (20)	30 (23)
3	102 (76)	97 (73)
Aortic stenosis	8 (6)	8 (6)
Hypertension	94 (70)	92 (70)
Previous myocardial infarction	38 (28)	42 (32)
Preoperative hemoglobin	144±13	143±14
Preoperative medications		
Aspirin	123 (92)	124 (94)
Clopidogrel	18 (13)	15 (11)
Diabetes mellitus	43 (32)	44 (33)
Educational level		
≤Grade 8	17 (6)	10 (4)
Grade 9–12	53 (20)	60 (23)
College/university	64 (24)	62 (23)

*Plus-minus values are mean±SD; others are no. (%).

CCS indicates Canadian Cardiovascular Society angina classification.

These tests were completed preoperatively and early (5 days) and late (3 months) postoperatively. Preoperative and postoperative measures of mood (Geriatric Depression Scale) and anxiety (State-Trait Anxiety Inventory) were obtained for use as covariates. Quality of life was assessed preoperatively and at 3 months using the Short Form Health Survey (Quality Metric Inc). There was no difference in either the Standardized Physical Component Scale or the Standardized Mental Component Scale of the Short Form Health Survey. The National Institutes of Health stroke scale was administered at each of the three neuropsychological assessments. The Canadian Neurological Scale²⁴ was used to detect neurological deficits on the first postoperative day. Patients with focal deficits underwent a complete neurological assessment, including CT scan, to document the injury.

Transcranial Doppler Measurements:

After induction of anesthesia, two 2-MHz transcranial Doppler probes were placed on the temporal windows to continuously detect high-intensity transient signals and velocity in the middle cerebral arteries. Doppler signals were recorded beginning 5 minutes before aortic cannulation and ending at the time of aortic decannulation. The sum of the count of high-intensity transient signals on the right and the left middle cerebral arteries represented the total microembolic count. Identification of high-intensity transient signals was performed manually according to their visual and acoustic properties following the standards of the Consensus Committee on emboli detection²⁵ and the reviewer was kept blinded to treatment assignment.

Objectives

The specific objective of the trial was to evaluate the effect of cardiomy blood centrifugation and filtration on intra- and postoperative blood loss and homologous transfusion requirements as well as early and late neurocognitive outcome in patients undergoing cardiac surgery with CPB.

Outcomes

The primary outcomes were the proportion of patients requiring one or more red blood cell (RBC) transfusions during the hospital stay as well as the incidence of neurocognitive deficit at 5 days. The secondary outcomes included blood loss (protamine administration to chest closure and first 24 hours), total non-RBC transfusion requirements (factors, platelets), quality of life, and the incidence of cognitive deficit at 3 months. We hypothesized that patients receiving processed cardiomy blood would experience fewer cognitive deficits after cardiac surgery and that processing may decrease bleeding attributable to removal of profibrinolytic factors in the blood.

Sample Size

The sample size was based on the proportion of patients requiring one or more RBC transfusions. We have reported an incidence of transfusion of 35% in historical control patients.²⁶ We proposed that a clinically important decrease would be a drop in this rate to 20% (a 42% decrease).²⁷ The sample size calculation was based on the formula for the comparison of independent proportions. Using a level of significance of 0.05 and power of 80%, the differences between transfusion rates for the control versus treatment groups could be detected with a sample of 137 per group. An interim analysis on the primary outcome (percent transfused) was completed by the Data Safety Monitoring Board when 50% the patients had completed the intervention. All clinical adverse events were reviewed by the Data Safety Monitoring Board and the Human Research Ethics Board.

Randomization: Sequence Generation, Allocation Concealment, Implementation

Randomization, supervised by the data manager, was computer-generated in blocks of 8 (SAS version 8.2; SAS Institute, Cary, NC) stratified for age (<75 years) and the assignment was concealed until the interventions were assigned. A sealed opaque envelope containing the treatment allocation was opened by the research coordinator just before the patient receiving heparin and the initiation of CPB. The perfusionist was informed of the treatment assignment.

Blinding

The patients, psychometrists, and all medical staff were blinded to treatment assignment. Intraoperative blinding of all members of the surgical team (except for the perfusionist) was accomplished by the positioning of an opaque drape over the CPB circuit and the cell saver.²⁸ All intraoperative decisions to transfuse during CPB were made by the anesthetist who was unaware of treatment assignment.

Statistical Analysis

Descriptive data are depicted as mean±SD for normally distributed variables and median [interquartile range] for variables not following a Gaussian distribution. Categorical variables are shown as the number (%). Data on coagulation profiles were analyzed using repeated measures analysis of variance. If the overall probability value from the analysis of variance F-test was <0.05, Bonferroni-corrected comparisons were made at individual time points. Because the primary end point of blood product use is a count variable with a highly skewed distribution, Poisson regression models were used to analyze these data.

Neuropsychometric Test Assessment

Principle components analysis with orthogonal rotation was used to derive 4 groupings of tests that were statistically independent of each other. For each domain, a composite score was derived by the procedure of Townes et al²⁹ in which each component score of the domain was standardized by subtraction of the mean and division by the SD of the corresponding preoperative scores for both groups combined. Individual raw scores were multiplied by -1 when necessary to give a common orientation. The mean of the standardized component scores was used as the score for the domain. A composite cognitive index was calculated by adding the 4 domain scores to yield a single, continuous measure of cognitive function.⁵ Patients were classified as cognitively impaired if they realized a decrease of ≥ 1.0 SD compared with preoperative values in one or more of the 4 domains.⁵ The incidence of POCD was compared by χ^2 test for all patients who completed the preoperative testing. All analyses of psychometric data were based on the intention-to-treat principle, by which all randomized patients were included in the analysis according to treatment assignment. When patients were unable to complete one, 2, or 3 of the tests or subtests at baseline or at follow up, we included data in the analysis for the tests they did not complete by imputing values. The group mean change score was added to the baseline test score to impute missing early and late postoperative data. Data for patients with more than 3 missing scores (21%) were not included in the analysis.

Analysis of covariance was used to test for a treatment effect at visit 2 and visit 3 using the preoperative test score as the covariate. All statistical analyses were performed using SAS version 9.1.

Statement of Responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the article as written.

Results

Participant Flow, Recruitment, Baseline Data, and Numbers Analyzed

The study was carried out between September 2001 and February 2006. Patient screening, enrollment, and follow-up data are presented in Figure 1. The treatment algorithm was successfully implemented in a blinded fashion in 266 patients (control [n=134], treatment [n=132]). Baseline characteristics were similar between treatment and control groups (Table 1). Data were collected from all patients on an intent-to-treat basis and no patients were lost to follow up for the bleeding and transfusion data. Preoperative neuropsychological testing was completed in 247 (93%) patients (control [n=125], treatment [n=122]). Complete bilateral transcranial Doppler recordings were obtained in 169 patients (control [n=86], treatment [n=83]). Transfusion protocol violations occurred in 9.9% of RBC transfusions (treatment 15 U, control 8 U).

TABLE 2. Neurocognitive Testing Results

	Control (n=125)			Experimental (n=122)		
	Preoperative	Change From Preoperative		Preoperative	Change From Preoperative	
		1 Week (n=118)	3 Months (n=113)		1 Week (n=117)	3 Months (n=108)
Psychomotor speed						
Trails A	34.78±13.35	0.92±10.63	-2.80±10.42	35.02±13.12	0.19±11.48	-2.91±10.37
Trails B*	82.60±45.57	11.27±31.28	-5.65±24.66	87.02±32.87	1.78±26.85	-7.72±29.38
Pegtime (dominant hand)	80.84±14.84	8.05±14.61	-4.13±16.38	79.99±16.10	7.53±14.43	-3.06±11.40
Pegtime (nondominant hand)	88.26±17.47	12.71±19.45	-3.91±15.25	89.02±19.61	10.85±18.12	-5.12±12.25
SDMT	48.38±10.24	-3.41±6.97	3.15±5.78	48.07±10.02	-2.63±7.08	1.69±5.82
Verbal Memory						
RAVLT						
Total (T1 to T5)	40.93±9.10	-1.60±7.31	0.96±7.54	42.02±9.18	-2.88±8.09	-1.00±6.72
Trial 6	8.07±3.06	-0.79±2.71	-0.50±2.37	8.25±3.15	-1.10±2.82	-0.16±2.35
Trial 7 (delayed recall)	7.77±3.11	-1.58±2.89	-0.61±2.67	7.68±3.26	-1.50±3.01	-0.15±2.51
Attention						
Digback	6.71±2.34	-0.36±1.77	0.19±1.88	6.20±2.24	-0.50±1.82	0.23±2.03
Digfor	10.12±2.22	-0.12±1.46	0.37±1.63	9.80±2.20	-0.12±1.61	0.53±1.78
Executive function						
Letter Fluency	33.43±11.31	1.02±7.67	1.98±7.46	33.27±11.52	0.89±7.53	1.89±7.23
Category Fluency (animal)	19.90±5.56	-1.75±5.14	-0.69±5.30	19.73±5.05	-1.25±4.45	0.26±4.34
Factor 1 Psychomotor Speed	0.005±1.015	-0.464±0.756	0.3±0.726	-0.005±0.988	-0.326±0.721	0.264±0.531
Factor 2 Verbal Memory	-0.03±0.98	-0.271±0.828	-0.153±0.785	0.031±1.024	-0.388±0.914	-0.145±0.733
Factor 3 Attention	0.101±1.007	0.044±0.648	0.155±0.658	-0.104±0.986	0.000±0.71	0.145±0.748
Factor 4 Executive Function	-0.001±1.037	0.023±0.816	-0.025±0.806	0.0013±0.956	0.105±0.838	0.072±0.762
Composite Cognitive Index	0.075±2.099	-0.669±1.157	0.277±0.916	-0.077±1.899	-0.609±1.060	0.336±0.890

All scores presented as mean±SD.

*Trails B P=0.0136, analysis of covariance.

1 week indicates early postoperative score-preoperative score; 3 month, 3-month score-preoperative score; SDMT, Symbol Digit Modalities Test; RAVLT, Rey Auditory Verbal Learning Test; Pegtime, Grooved pegboard; Digfor, Digit Span Forward; Digback, Digit Span Backward.

TABLE 3. Depression and Anxiety Scores

	Control (n=125)			Experimental (n=122)		
	Preoperative	Change From Preoperative		Preoperative	Change From Preoperative	
		1 Week (n=118)	3 Months (n=113)		1 Week (n=117)	3 Months (n=108)
GDS	3.5±2.8	0.4±2.5	-1.4±2.8	3.2±2.8	0.5±3.0	-1.1±3.0
STAI-state	37±11	0.6±12.0	-8.0±12.0	36±10	-1.3±11.0	-6.0±11.0
STAI-trait	34±9	0.6±7.0	-2.6±5.9	34±9	-0.8±7.0	-2.9±8.0

GDS indicates Global Deterioration Scale; STAI, State-Trait Anxiety Inventory.

Outcomes and Estimation

Neurocognitive Outcomes

At the time of discharge, the incidence of POCDs was 45.3% in the treatment group and 39.0% in control subjects (Table 2, relative risk: 1.16, 95% CI: 0.86 to 1.57). The number of patients with cognitive deficits was significantly lower at 3-month follow up with no significant differences between groups (16.7% versus 15.9%, treatment versus control, relative risk: 1.04, 95% CI: 0.58 to 1.90). During analysis of individual neurocognitive tests, only one (Trails B) demonstrated significant differences between groups. However, after adjusting for multiple comparisons, this difference was not statistically significant. There was no difference in the Composite Cognitive Index between groups (Table 2) nor was there any difference between the groups in measures of anxiety and depression (Table 3). There was a significant improvement in both physical and mental measures of quality of life 3 months after surgery with no significant differences between groups (Table 4).

Postoperative Bleeding and Transfusions

The proportion of patients transfused was higher in the treatment group (42% versus 36%), but this did not reach statistical significance ($P=0.27$). Overall, patients in the treatment group demonstrated increased RBC (1.24 ± 2.71 versus 0.81 ± 1.24 U/patient, $P=0.001$) and non-RBC (2.06 ± 7.70 versus 1.12 ± 4.74 U/patient, $P<0.001$) transfusions. Blood loss from protamine administration to skin closure was not different between groups (control 185 ± 159 mL, treatment 156 ± 131 mL, $P=0.10$). Postoperative chest tube output was significantly higher in the treatment group (control 1014 ± 420 mL/24 hours, treatment 1133 ± 476 mL/24 hours $P=0.04$), excluding patients who were reopened for bleeding. There was no significant difference in the full cohort of 266 randomized patients (control 1138 ± 613 mL/24 hours, treatment 1197 ± 574 mL/24 hours).

Coagulation Parameters

Hemoglobin levels in the pre- and perioperative period and at discharge (Table 3) were similar between groups. Platelet count was also similar between groups but showed a trend to be slightly lower in the treatment group 12 hours after CPB ($P=0.05$). After CPB, the treatment patients demonstrated significant abnormalities in multiple coagulation parameters compared with control patients. Partial thromboplastin time and international normalized ratio levels were significantly higher 2 hours post-CPB (both $P<0.01$) and remained elevated until 12 hours post-CPB (Figure 2A–B). Similar but less pronounced increases in thrombin time and reductions in fibrinogen levels were also observed in treatment patients (Figure 2C–D).

Transcranial Doppler

There was no difference in the total number of high-intensity transient signals in the 2 groups (control 246, 95% CI: 195 to 298; treatment 213, 95% CI: 169 to 258).

Intraoperative and Postoperative and Safety Data

Intraoperative data are depicted in Table 5. The amount of cardiomy blood collected was also similar between groups (P =not significant, control 605 mL 95% CI: 518 to 692; treatment 636 mL, 95% CI: 566 to 706; total 636 mL 95% CI: 566 to 706). After centrifugation, washing, and filtration in the treatment group, the volume returned was 281 ± 28 mL.

There were no significant differences between groups with respect to major morbidity (Table 6). There were 17 reopenings (Control 11, treatment 6, P =not significant) with surgical sites of bleeding identified in 10 and coagulopathy in 3, but undetermined cause in 4 cases. There were no instances of adverse events that were deemed by the Data Safety Monitoring Board to be secondary to the interventions.

TABLE 4. Quality-of-Life Measurements

	Control		Treatment	
	Preoperative	Change from Preoperative to 3 Months Postoperative	Preoperative	Change From Preoperative to 3 Months Postoperative
MCS	49.7±9.8	5.6±9.9*	50.7±9.9	3.5±9.7†
PCS	34.6±10.0	11.0±10.9*	35.6±9.5	9.0±11.4*

* $P<0.0001$.

† $P=0.0069$.

MCS indicates standardized mental change score; PCS, standardized physical change score.

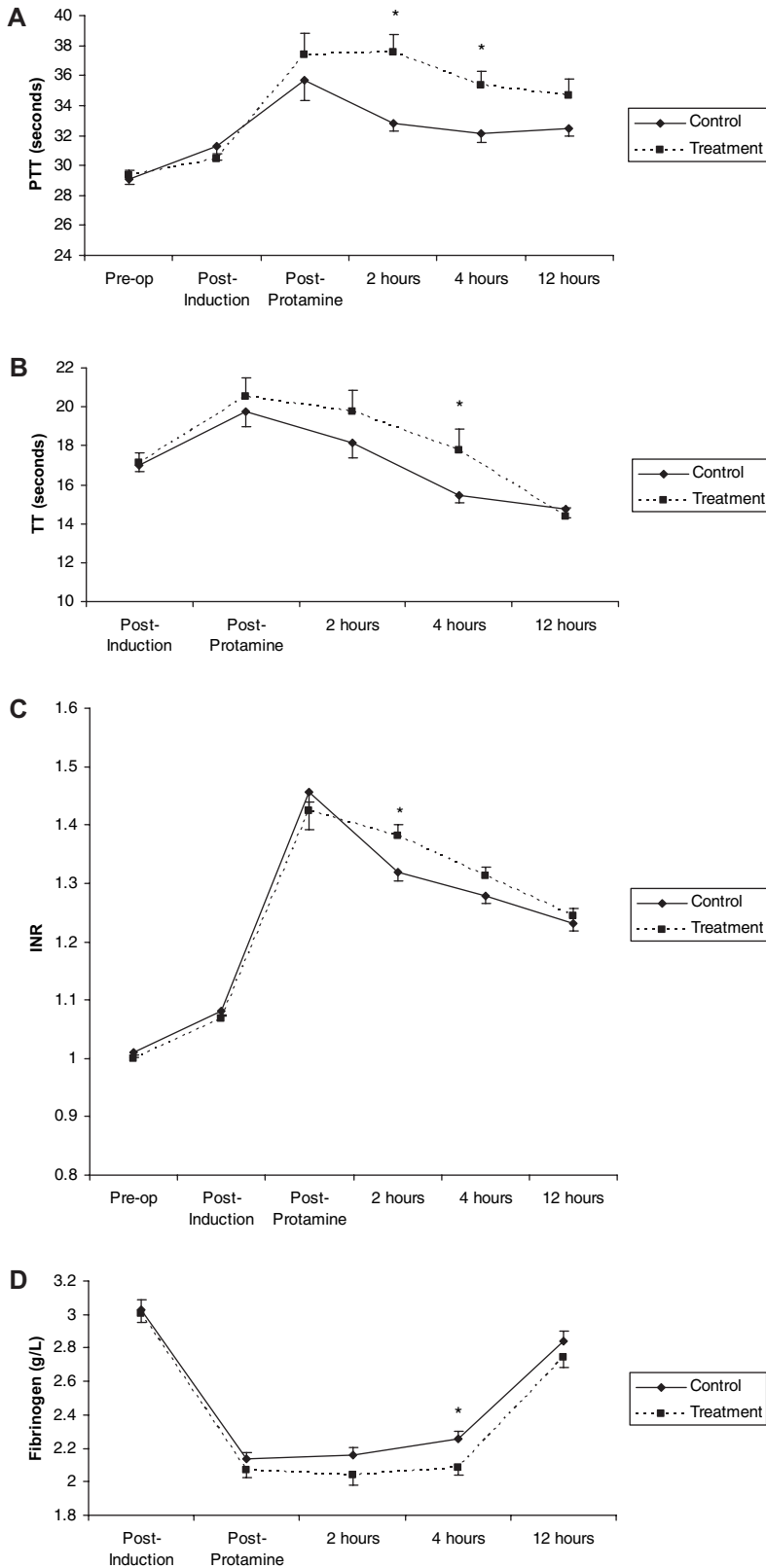


Figure 2. Coagulation measurements at various time points in treatment and control groups. A, Partial thromboplastin time (PTT), (B) international normalized ratio (INR), (C) thrombin time (TT), (D) fibrinogen. Data were analyzed using repeated measures analysis of variance. * $P < 0.05$ after adjusting for multiple comparisons.

Discussion

Although the proportion of patients transfused was not different between the control and treatment groups, processing of cardiomy blood resulted in a significant increase in postoperative bleeding and mean blood use. These outcomes

were associated with significant derangements in international normalized ratio, thrombin time, and partial thromboplastin time, suggesting that a loss of plasma coagulation proteins during the centrifugal washing process likely contributed to the bleeding. There was no difference in the

TABLE 5. Intraoperative Data

	Control (n=134)	Treated (n=132)	P
Procedure: CABG	125	124	0.77
CABG +AVR	7	5	
AVR	2	3	
CPB time, minutes	88±2	87±2	0.76
Cardiac anoxia time, minutes	62±2	59±2	0.27
Total no. distal anastomoses	3.0±0.1	3.1±0.1	0.76
Conduits: RITA	84 (63)	75 (57)	0.33
LITA	126 (94)	124 (94)	0.98
Radial	54 (40)	63 (48)	0.22
Heparin, units±SD	40200±800	41700±900	0.20
Protamine, mg±SD	338±58	342±70	0.62
Total crystalloid, mL	5360±144	5274±129	0.66
Total colloid, mL	274±29	304±34	0.50

CABG indicates coronary artery bypass grafting; AVR, aortic valve replacement; CPB, cardiopulmonary bypass; RITA, right internal thoracic artery; LITA, left internal thoracic artery.

incidence of POCD between the 2 groups either early (5 days) or late (3 months) after surgery, nor was there a benefit in terms of quality of life. There was no difference in the number of high-intensity transient signals in the 2 groups as measured by transcranial Doppler.

The management of cardiomy blood is an integral part of the practice of all cardiac surgical procedures involving CPB. During routine nonreoperative coronary artery bypass, the volume of cardiomy blood has been previously estimated to range between 700 and 1200 mL.¹⁸ The current report includes documentation of the average amount of cardiomy blood collected during routine coronary artery bypass grafting (636±577), which is consistent with previous reports.¹⁹

The Cardiomy Trial represents the largest prospective, randomized study addressing the clinical consequences related to the processing of cardiomy blood during CPB. Effective steps were taken to ensure blinding of the patients and all surgical and medical team members to avoid bias in outcomes, and transfusion protocol compliance was excellent. A recent evidence-based review of CPB practice³⁰ has concluded that the direct reinfusion of unprocessed cardiomy

TABLE 6. Postoperative Data

	Control (n=134)	Treated (n=132)	P
Hospital mortality, no. (%)	2 (1.5)	2 (1.5)	0.99
Postoperative inotropes, no. (%)	17 (13)	17 (13)	0.96
IABP, no. (%)	2 (1.5)	1 (0.8)	0.38
Ventilation time, hours±SD	17±43	13±33	0.50
ICU stay, days±SD	1.6±2.1	1.6±2.3	0.87
In-hospital stay, days±SD	6.4±3.3	6.6±4.6	0.63
Atrial fibrillation, no. (%)	34 (28)	37 (30)	0.70
Postoperative infection, no. (%)	4 (3.0)	6 (4.6)	0.50
Discharge hemoglobin, g/dL±SD	98.5±1.1	97.6±1.0	0.54

IABP indicates intraaortic balloon pump; ICU, intensive care unit.

omy blood should be avoided (Class I recommendation, Level B level of evidence)³¹ and that blood cell processing and secondary filtration can be considered to decrease the deleterious effects of reinfused shed blood (Class IIb, Level B). Our results do not support these recommendations. The findings in this trial also do not concur with those reported by De Haan et al in which patients undergoing CPB were randomly assigned to have cardiomy blood either reinfused or discarded.¹⁸ They reported that reinfusion of cardiomy blood increased postoperative bleeding with a trend to increase homologous blood transfusions. We believe this trial may have been compromised by the lack of blinding and a transfusion protocol.

The current data support the scrutiny that is developing with regard to the contribution of CPB to POCD after cardiac surgery. Although we have previously demonstrated an improvement in neurocognitive function with careful temperature management during CPB,³² no other interventions during CPB have been associated with such a clear neurological benefit. Avoidance of CPB with off-pump surgery has not been shown to improve short³³ or long-term³⁴ neurocognitive function. Furthermore, recent studies comparing on-pump coronary artery bypass grafting to percutaneous intervention have shown little difference in cognitive outcome.³⁵

Potential limitations of the current trial were primarily related to the inclusion criteria because some high-risk cases and cases involving reoperative surgery were excluded. As a result of the small number of aortic valve cases that were recruited, the strict application of these results to valve surgery may not be entirely supported; however, there is little theoretical justification to expect that these findings would not be similar. Lastly, we believe the intervention strategy tested in the treatment group involved the best clinically and commercially available approach that was most relevant to surgeons' practices.

In conclusion, routine centrifugal processing of cardiomy blood during CPB results in increased postoperative bleeding and increased transfusion requirements. In the absence of a proven benefit in terms of neurological protection or hemodynamic stability, we believe that there is little to justify the routine use of this technique.

Appendix

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Sources of Funding

This trial was funded by Clinical Trials Grants MCT-44149 and MCT-70887 from the Canadian Institute of Health Research.

Disclosures

The LeukoGuard RS filters were provided by Pall Biomedical (East Hills, NY).

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