Limitation of thrombin generation, platelet activation, and inflammation by elimination of cardiotomy suction in patients undergoing coronary artery bypass grafting treated with heparin-bonded circuits

Gabriel S. Aldea, MD
 Louise O. Soltow, BS
 Wayne L. Chandler, MD
 Christopher M. Triggs, PhD*
 Craig R. Vocolka, CCP
 Gregory I. Crockett, CCP
 Yong T. Shin, MD
 William E. Curtis, MD
 Edward D. Verrier, MD

Objective: Reports evaluating the efficacy of heparin-bonded circuits to blunt inflammation, platelet dysfunction, and thrombin generation in response to cardiopulmonary bypass have varied. We hypothesized that this variability may in part be related to the use of cardiotomy suction, which has been demonstrated to reintroduce procoagulant and proinflammatory factors into the systemic circulation during cardiopulmonary bypass. A prospective, randomized study was undertaken to evaluate the specific effects of cardiotomy suction.

Methods: Thirty-six patients undergoing first-time, nonemergency coronary artery bypass grafting with cardiopulmonary bypass were randomly assigned to one of three treatment groups: group I, non-heparin-bonded circuits with the use of cardiotomy suction ($n = 12$); group II, Duraflo II (BCR-3500; Jostra Bentley Corp, Irvine, Calif) heparin-bonded circuits with cardiotomy suction ($n = 12$); and group III, Duraflo II heparin-bonded circuits without cardiotomy suction ($n = 12$). Thrombin generation, neutrophil activation (polymorphonuclear elastase), platelet activation (β -thromboglobulin), and neuronal injury (neuron-specific enolase) were analyzed by enzyme-linked immunosorbent assays after cardiopulmonary bypass and compared with prebypass levels. Results are presented as mean $\pm$ SEM.

Results: Prebypass levels of all markers were similar among treatment groups. However, postbypass levels were significantly and consistently highest in group I relative to groups II and III. Thrombin generation levels were 5.0 ± 0.9 nmol/L in group I, 3.0 ± 0.6 nmol/L in group II, and 1.5 ± 0.1 nmol/L in group III ($P < .05$ vs group II and $P < .001$ vs group I). Polymorphonuclear elastase levels were 307 ± 64 μ g/L in group I, 128 ± 24 μ g/L in group II ($P < .05$ vs group I), and 75 ± 14 μ g/L in group III ($P < .001$ vs group I). β -Thromboglobulin levels were 2692 ± 401 IU/mL in group I, 912 ± 99 IU/mL in group II ($P = .001$ vs group I), and 646 ± 133 IU/mL in group III ($P = .001$ vs group I). Neuron-specific enolase levels were 9.8 ± 0.9 ng/mL in group I, 10.5 ± 1.6 ng/mL in group II, and 4.2 ± 0.5 ng/mL in group III ($P = .001$ vs groups I and II).

Conclusions: Use of cardiotomy suction resulted in significant increases in thrombin, neutrophil, and platelet activation, as well as the release of neuron-specific enolase, after cardiopulmonary bypass. Limiting increases in these markers would be best accomplished by eliminating cardiotomy suction and routinely using heparin-bonded circuits whenever possible.

From the Division of Cardiothoracic Surgery, Department of Surgery, University of Washington School of Medicine, Seattle, Wash.

Read at the Twenty-seventh Annual Meeting of The Western Thoracic Surgical Association, San Diego, Calif, June 20-23, 2001.

Received for publication May 5, 2001; revisions requested July 9, 2001; revisions received Aug 27, 2001; accepted for publication Sept 16, 2001.

Address for reprints: Gabriel S. Aldea, MD, Associate Professor, Division of Cardiothoracic Surgery, Department of Surgery, University of Washington, PO Box 356310, 1959 NE Pacific St, Seattle, WA 98195-3166 (E-mail: aldea@u.washington.edu).

* Visiting Professor in the Department of Statistics, University of Washington, from the University of Auckland, New Zealand.

J Thorac Cardiovasc Surg 2002;123:742-55

Copyright © 2002 by The American Association for Thoracic Surgery

0022-5223/2002 \$35.00+0 12/6/120347

doi:10.1067/mtc.2002.120347

Heparin-bonded circuits (HBCs) have been demonstrated to blunt complement, neutrophil, and platelet activation as well as fibrinolysis and chemokine and cytokine expressions in patients undergoing coronary artery bypass grafting (CABG).¹⁻⁷ The clinical significance of these blunted responses is still being debated.⁸ Many clinicians believe that these markers are of scientific interest but little clinical relevance. Clinically the use of HBCs has been associated with reductions in postoperative bleeding, transfusion requirements, need for inotropic support, pulmonary dysfunction, and thromboembolic complications.^{4,9-14} These improvements translate to decreased intensive care unit (ICU) and hospital stays and therefore to decreased cost.⁹ Our previous work documented that these improvements were due both to the use of HBCs and to a lower anticoagulation protocol.¹⁰ All studies to date have demonstrated that HBCs are safe. Although some clinical trials demonstrated improvement in clinical outcomes in all patients undergoing CABG,^{4,9-14} however, other trials have demonstrated more modest clinical improvements only in higher-risk patient populations.¹⁵⁻¹⁷

We hypothesized that the difference in the reported efficacy of HBCs and observed clinical outcomes may be due to variations in cardiopulmonary bypass (CPB) techniques between institutions. Specifically, we hypothesized that the use of cardiotomy suction may significantly and adversely impact the pathophysiologic perturbations noted in responses to CPB. The potential clinical benefits associated with HBCs may not be evident when cardiotomy suction is used routinely, because cardiotomy suction may directly contribute to elevations in markers of inflammation, platelet activation, and thrombin generation. Recent animal and human studies documented that cardiotomy suction may result in platelet activation, thrombin generation, and release of inflammatory cytokines.¹⁸⁻²³ In addition, mediastinal debris (primarily fat emboli) may be introduced into the CPB circuit and the systemic circulation.¹⁸ This fat easily deforms and is not eliminated by arterial filters. Embolization of atherosclerotic aortic debris, fat, and defoaming agents, as well as inflammation leading to central nervous system edema, have been implicated as causes of neurologic and neuropsychologic dysfunction after valve and CABG procedures. These injuries have been associated with elevations in markers of neuronal injury, including serum glial protein (S100 β) and neuron-specific enolase (NSE).²⁴⁻³³ This prospective, randomized trial was designed to assess and disassociate the independent effects of the use of HBCs and cardiotomy suction on plasma markers of inflammation, thrombin generation, and platelet activation, as well as serum markers of neurologic injury, in patients undergoing CABG with CPB.

Patients and Methods

Study Design

The protocol was reviewed and approved by the human subjects institutional review boards at the University of Washington and Northwest Hospital. Informed consent was obtained with adherence to guidelines set forth in the Helsinki Declaration. Patients were included if the following criteria were met: (1) they were undergoing primary, nonemergency, on-pump CABG revascularization; (2) they were at least 18 and less than 90 years of age; and (3) they did not have a preoperative intra-aortic balloon pump or assist device. Patients were excluded from the study for the following reasons: (1) left ventricular ejection fraction less than 25%, (2) allergy to heparin or heparin-induced thrombocytopenia, (3) steroid treatment, (4) inability to perform the neuropsychologic test battery, (5) other vascular surgery planned with the CABG (such as aortic arch, carotid endarterectomy, or ventricular aneurysmectomy), (6) dementia, (7) alcohol or drug abuse, (8) hereditary complement deficiency, (9) any serious medical condition that would bias the study or endanger the patient with respect to taking part in the study, and (10) inability to fully understand any of the aspects of the protocol or provide informed, written consent.

Prognostic factors, such as pulmonary hypertension, congestive heart failure, chronic obstructive pulmonary disease, diabetes, previous myocardial infarction, and preoperative anticoagulant or antiplatelet agents, were noted. Demographic and cardiac variables (age, sex, height, weight, left ventricular ejection fraction, body surface area, Canadian Classification System class, and New York Heart Association functional class) were also noted. Operative and postoperative variables were tabulated for later analysis across groups.

The study design involved random assignment of each subject to one of three treatment arms: group I, non-HBCs with cardiotomy suction; group II, HBCs with cardiotomy suction; and group III, HBCs with cardiotomy suction eliminated. The numbers of subjects in the three treatment groups were based on a power calculation from previous laboratory data that demonstrated a 50% reduction in markers for coagulation (prothrombin fragments 1.2 [PF1.2], thrombin-antithrombin) and inflammation (interleukin-8, polymorphonuclear elastase [PMNE]) with use of HBCs. A computer-generated randomization scheme was produced by the investigational drug pharmacist before the study. Patients undergoing primary, nonemergency CABG were enrolled into the study after giving written consent. Patients were assigned to one of three study groups by the perfusionist on the basis of the randomization scheme. Clinical pathways leading to transfusion, weaning from ventilator support, discharge from the ICU, and hospital were standardized. The postoperative team was blinded to treatment group assignment.

Cardiotomy Suction Versus No Cardiotomy Suction: Bypass Equipment

Group I. Suctioned cardiotomy blood was forwarded from the field to hard-shell, non-heparin-coated cardiotomy reservoirs (COBE 09F4798; COBE Cardiovascular, Inc, Arvada, Colo), as was vented blood from the aorta. The CPB circuit was composed of a non-heparin-coated hard-shell venous reservoir with peristaltic pump and membrane oxygenators (AFFINITY CVR model 2000; Medtronic Perfusion Systems, Minneapolis, Minn).

Group II. Suctioned cardiomy blood was forwarded from the field to hard-shell, heparin-coated, cardiomy reservoirs (Durafllo II BCR-3500; Jostra Bentley Corp, Irvine, Calif), as was vented blood from the aorta. The CPB circuit was composed of heparin-coated, collapsible, soft-shell venous reservoirs (BMR-1900; Jostra Bentley) with centrifugal pumps (Sarns Centrifugal System; Terumo Cardiovascular Systems, Corp, Ann Arbor, Mich) and membrane oxygenators (Spiralgold, Jostra).

Group III. Suctioned blood from the field was directed to the cell saver (COBE BRAT II). Vented aortic blood was directed to a heparin-coated, collapsible, soft-shell venous reservoir (BMR-1900), as was vented blood from the aorta. The CPB circuit was composed of a centrifugal pump (Sarns Centrifugal System) and a heparin-coated membrane oxygenator (Spiralgold).

All groups. Activated clotting times (ACTs) were maintained at longer than 450 seconds in all three groups during CPB. Cell-saving equipment (COBE BRAT II) was used in all three groups, but with different treatment strategies. In groups I and II cell saving was used before and after completion of CPB. In group III the cell saver device was used throughout the surgical procedure (including CPB). Cardiomy suction was used in groups I and II for the duration of CPB. Adequate anticoagulation was verified every 15 minutes with the Heparin Management System (Medtronic Perfusion Systems).

Transfusion protocol was directed by strict adherence to clinical pathways. Patients were transfused with packed red blood cells for a hematocrit less than 20% on CPB and less than 25% after CPB. Platelets and appropriate transfusion factors were administered in the postoperative period on the basis of laboratory and coagulation data and for chest tube output exceeding 200 mL/h. Processed blood from the cell saver was administered after CPB and protamine administration in all cases.

Anesthesia and Extracorporeal Circulation

Anesthesia techniques were consistent across the three study groups. Anesthesia induction and maintenance were performed with fentanyl (initial intravenous bolus of 250 μ g followed by an intravenous infusion of 1.8–2.4 μ g/[kg $\cdot$ h]), midazolam (5–10 mg at induction), pancuronium, and etomidate. Isoflurane (0.5%–1.5%) was used during the operation. Propofol (10 mL/h) was used after CPB and in the ICU for sedation. Prophylactic antifibrinolytic treatment with ϵ -aminocaproic acid (Amicar) was routinely used; a 10-g intravenous load was followed by an intravenous infusion of 5 to 10 g/h throughout the operation. No aprotinin was administered.

Bypass circuits were primed with Plasmalyte (Baxter Healthcare Corporation, Deerfield, Ill). The intravenous heparin load and pump prime doses were based on an ACT target of 450 seconds and calculated with the heparin dose-response assay (Hepcon Instrument; Medtronic Perfusion Systems). During CPB additional heparin was administered if the ACT fell below 450 seconds. The pump flow rate was established at more than 2.4 L/(min $\cdot$ m²). Blood cardioplegia and formulation techniques were uniform among the three treatment groups. Minimal, systemic normothermia was used; lowest bladder temperatures were usually between 34°C and 36°C. Patients' mean arterial pressures were maintained at a minimum of 60 mm Hg with either phenylephrine or isoflu-

rane, as needed. Processed cell saver contents were administered intravenously after cessation of CPB.

Rewarming to 37°C was undertaken before weaning from CPB. The protamine dose was calculated on the basis of the heparin concentration at the conclusion of CPB with the Hepcon system. A 1:1 ratio of heparin to protamine was used.

Neuropsychologic Assessments

Neuropsychologic assessments were performed on subjects before the operation in the clinic or on the hospital wards. Postoperative testing was done at hospital discharge. A small battery of tests for memory (Rey Auditory Verbal Learning Test [RAVLT]), symbol discrimination and processing (Symbol Digit Modality Test [SDMT]), visual acuity (Clock Drawing), and ability to categorize (Category Fluency–Animals) were performed. Scores at discharge visits were subtracted from baseline scores on a per patient basis.

Blood Sampling

Blood samples for laboratory marker analyses were drawn from radial artery line. Blood samples were drawn at baseline (after anesthesia induction, before bypass), at 5 minutes on bypass, after bypass (just after protamine), 4 hours after bypass, and on the first postoperative day. Blood samples were obtained by venipuncture on postoperative day 2.

Laboratory Assays

Laboratory markers for inflammation (PMNE), interleukin (IL) 6 and IL-8, coagulation (PF-1.2), platelet activation (β -thromboglobulin [β -TG], platelet factor 4 [PF-4], soluble P-selectin), terminal complement activation (C5_{b-9}), neuronal injury (NSE, S100 β) and fibrinolysis (tissue-type plasminogen activator [tPA], plasminogen activator inhibitor [PAI-1]) were assayed in all study patients. For PF-1.2 measurements, blood was collected into (FPR-chloromethylketone) sodium citrate (PPAK) tubes and plasma was assayed by a monoclonal antibody–sandwich enzyme-linked immunoassay (ELISA) technique (Enzygnost F1+2 Micro; Dade Behring Marburg GmbH, Marburg, Germany). For PMNE, citrated plasma was assayed with a heterogeneous enzyme immunoassay composed of a complex between PMNE and α -proteinase inhibitor followed by binding of alkaline phosphatase antibodies to the α -P1 end of the complex, which was measured photometrically (Merck kit from EM Science, Gibbstown, NJ). IL-6 was assayed from ethylenediaminetetraacetic acid (EDTA)–prepared plasma by ELISA (catalog Nos. MAb 206 and BAF-206, R&D Systems, Inc, Minneapolis, Minn; catalog No. A2004, Vector Laboratories, Inc, Burlingame, Calif). IL-8 was also assayed from EDTA-prepared plasma by ELISA (catalog Nos. M801 and M802-B, Endogen, Inc, Woburn, Mass; catalog No. A2004, Vector). For PF-4 and β -TG measurements, blood was collected into previously cooled tubes containing a solution of citric acid, theophylline, adenosine, and dipyrindamole, and plasma was assayed by ELISA (Diagnostica Stago). P-selectin was measured in citrated plasma by ELISA (catalog No. BBE 6; R&D Systems). tPA activity was assayed using monoclonal antibody to tPA (SP-322) followed by chromogenic detection of the plasmin-sensitive substrate (catalog No. 1103, Biopool, Inc, Umea, Sweden). tPA activity was assayed using plasma prepared from blood collected into Stabilyte tubes (Biopool), which are necessary to prevent PAI-1 from quenching

TABLE 1. Demographic and preoperative data

Variable	Group I (n = 12)	Group II (n = 12)	Group III (n = 12)
Age (y)	66 ± 10	65 ± 11	65 ± 8
Gender (male/female ratio)	8:4 (67%:33%)	9:3 (75%:25%)	11:1 (92%:8%)
Body surface area (m ²)	2.01 ± 0.2	2.02 ± 0.18	2.08 ± 0.17
Left ventricular ejection fraction (%)	50 ± 9	54 ± 15	48 ± 9
Hypertension	11/12 (92%)	12/12 (100%)	11/12 (92%)
Diabetes mellitus (dietarily controlled plus insulin-dependent plus non-insulin-dependent diabetes)	3/12 (25%)	2/12 (17%)	3/12 (25%)
Previous cerebrovascular accident	3/12 (25%)	1/12 (8%)	1/12 (8%)
Previous myocardial infarction	4/12 (33%)	4/12 (33%)	4/12 (33%)
Chronic obstructive pulmonary disease	2/12 (17%)	3/12 (25%)	3/12 (25%)
Previous use of anticoagulants	9/12 (75%)	8/12 (58%)	7/12 (58%)

Data are expressed as mean ± SD for continuous variables and as number affected/number in group and percentage in group for categorical variables. *P* values are based on ANOVA with Scheffé post hoc tests or χ^2 for categorical variables; all comparisons *P* > .20.

TABLE 2. Operative data

Variable	Group I (n = 12)	Group II (n = 12)	Group III (n = 12)	<i>P</i> value		
				I vs II	I vs III	II vs III
CPB time (min)	80 ± 27	87 ± 29	82 ± 21	>.20	>.20	>.20
Crossclamp time (min)	59 ± 23	70 ± 27	68 ± 21	>.20	>.20	>.20
No. of grafts	3.5 ± 1.0	3.5 ± 1.2	3.8 ± 0.9	>.20	>.20	>.20
ACT average mid CPB (s)	459 ± 50	475 ± 55	477 ± 110	>.20	>.20	>.20
Cell saver volume (mL)	786 ± 201	815 ± 161	999 ± 251	>.20	.056	.11

Operative variables are expressed as mean ± SD. *P* values are based on ANOVA with Scheffé test.

tPA activity in the sample. PAI-1 activity was measured in citrated plasma with an immunofunctional method. Plasma was added to microtiter plates coated with active tPA. Active PAI-1 in the sample bound to the active tPA to form tPA/PAI-1 complex, which was measured with an anti-PAI-1-horseradish peroxidase conjugate (Chromolize PAI-1; Biopool).

For C5_{b-9} measurements, EDTA-treated plasma was assayed by ELISA (catalog No. A009, QUIDEL Corporation, San Diego, Calif). NSE and S100 β were measured in serum by ELISA (SMART Kits; Skye PharmaTech Inc, Mississauga, Ontario, Canada). All laboratory data are reported as back-transformed log₁₀ mean and log₁₀ mean ± SEM.

Statistical Analysis

Comparison of laboratory data across the three treatment groups, primarily after bypass, the point at which most laboratory markers peaked, was performed by analysis of variance (ANOVA), with the Scheffé test used for multiple comparisons among the three treatment groups. Increases in laboratory markers with time relative to baseline levels were evaluated by ANOVA for repeated measures. SPSS statistical software (version 8.0; SPSS Inc, Chicago, Ill) was used. Laboratory data were scrutinized for normality by means of normal probability Q-Q plots and log-transformed before ANOVA procedures to stabilize variance between the groups.

Demographic and clinical variables were analyzed by ANOVA for continuous variables or the χ^2 test for categorical variables. Data were tabulated as mean ± SD for continuous data or number

of cases and percent of total in each group for categorical data. Bleeding and transfusion data were compared by nonparametric methods (Kruskal-Wallis test) followed by ANOVA with Scheffé test.

Laboratory data were tested for correlations by the Pearson correlation coefficient. Neuropsychologic data were analyzed by applying ANOVA to differences between baseline and follow-up scores.

Results

After institutional review board approval to proceed with the research was obtained, 42 subjects gave written consent to participate in the research study from April 1, 2000, to March 30, 2001. Six subjects were excluded before or during the operation because autologous blood from the cell saver was transfused during the operation, the time frame of surgery changed, the subject withdrew before the operation, the heparinization protocol was not followed, or a ventricular aneurysm was discovered during the operation. Demographic data on 36 evaluable subjects, 12 subjects per group, showed no differences between groups (Table 1). Prognostic variables were distributed evenly across treatment groups. Operative data were scrutinized for adherence to the heparinization scheme, and no differences were evident between groups except for cell saver volume at the end of CPB, which was significantly greater (by approximately

TABLE 3. Transfusion data

	Packed red blood cells	Platelets	Total donor units
Group I (n = 12)			
No. of units transfused (mean $\pm$ SD)	2.8 $\pm$ 2.3	3.0 $\pm$ 4.0	8.2 $\pm$ 6.6
No. of units transfused (median)	2	0	7
Percentage of homologous units transfused	83	33	100
Group II (n = 12)			
No. of units transfused (mean $\pm$ SD)	1.8 $\pm$ 1.8	0.5 $\pm$ 1.7	2.3 $\pm$ 2.9
No. of units transfused (median)	2	0	2
Percentage of homologous units transfused	58	8	58
Group III (n = 12)			
No. of units transfused (mean $\pm$ SD)	1.7 $\pm$ 1.5	0.0 $\pm$ 0.0	1.7 $\pm$ 1.5
No. of units transfused (median)	1.5	0	1.5
Percentage of homologous units transfused	67	0	67
<i>P</i> value			
I vs II	>.20	.069	.007
I vs III	>.20	.024	.003
II vs III	>.20	>.20	>.20

Kruskal-Wallis test and ANOVA used.

200 mL) in group III than in groups I and II (Table 2). All other perfusion variables (total crystalloid pump prime, cardioplegia and heparin doses, protamine reversal dose, and heparin levels during CPB) were not different between groups (data not shown).

Clinical End Points

Chest tube output measured at 24 hours was not different between groups (data not shown). Homologous transfusions, represented as total homologous donor units, were reduced by 5.9 units in group II versus group I ($P = .007$) and 6.5 units in group III versus group I ($P = .003$, medians 7.0 vs 2.0 vs 1.5 units for groups I, II, and III, respectively; Table 3). Most transfusions were administered in the first 24 hours after CABG. Of the patients who received transfusions, 70% in group I (n = 7/10), 71% in group II (n = 5/7), and 100% in group III (n = 8/8) were transfused within the first 24 hours. Baseline hematologic characteristics were similar between treatment groups. Hematocrit and hemoglobin were lower on average in group I immediately after CPB and on postoperative day 2 than in groups II and III but were similar at hospital discharge, despite differences in the transfusion rates (Table 4). Platelet counts were also lower on average in group I after CPB but similar by discharge across groups, suggesting adherence to the transfusion protocol.

Coagulation was better preserved after CPB in group III than in groups I and II, as reflected by platelet count, fibrinogen, and thromboelastography (TEG), a measure of clot strength. Fibrinogen was similar at baseline but higher by approximately 70 mg/dL in group III than groups I ($P = .023$) and II ($P = .038$) immediately after CPB.

TEG values for three of the four measured parameters

(r , κ , α , and maximum amplitude [MA]) were more nearly in the reference range in group III than in groups I and II. TEG κ was lower by approximately 1.2 mm in group III than in groups I ($P = .09$) and II ($P = .043$). TEG MA, the main gauge of clot strength, was higher by approximately 6 to 8 mm (>59 mm is normal) in group III than in groups I ($P = .016$) and II ($P = .001$). Finally, the angle (TEG α) was higher ($>64^\circ$ is normal) in group III than in groups I and II ($P = .01$). Results of clinical chemistry panels performed throughout the hospital stay were similar between groups (data not shown).

Postoperative duration of ventilatory support was lower by 3.0 hours in group III than in groups I and II, but this difference did not reach statistical significance ($P > .20$; Table 5). Complications and hospital stay were also similar between groups. One subject in group I, who was at extremely high risk for central nervous system complications, died 3 weeks after CABG of a dense cerebrovascular accident after a coronary angiogram to evaluate atypical chest pain. One subject in group I returned to the operating room because of postoperative bleeding.

Laboratory Results

Baseline levels of all laboratory markers studied were determined and showed no differences between groups except for tPA, which was lower by 0.4 U/mL in group I than in group II ($P = .02$). All markers increased significantly and peaked immediately after CPB, except for IL-6 and P-selectin, which peaked 4 hours after CPB.

Thrombin generation (PF-1.2) was reduced by 3.5 nmol/L in group III relative to group I ($P < .001$) and by 1.5 nmol/L relative to group II ($P = .042$) at the post-CPB time point (Table 6, Figure 1). Consistent with other reports, tPA

TABLE 4. Clinical laboratory data

	Group I (n = 12)	Group II (n = 12)	Group III (n = 12)	P value		
				I vs II	I vs III	II vs III
Hematocrit (%)						
Baseline	40.7 ± 3.8	42.8 ± 3.2	41.0 ± 4.4	>.20	>.20	>.20
After CPB (in operating room)	25.3 ± 2.3	27.1 ± 2.9	26.6 ± 3.8	>.20	>.20	>.20
Postoperative day 2	24.9 ± 3.3	28.3 ± 3.0	27.2 ± 2.9	.062	>.20	>.20
Postoperative day 4 or discharge	28.2 ± 3.4	29.2 ± 2.5	28.4 ± 2.7	>.20	>.20	>.20
Hemoglobin (g/dL)						
Baseline	13.6 ± 1.7	14.6 ± 0.9	13.9 ± 1.3	>.20	>.20	>.20
Postoperative (ICU)	11.1 ± 1.4	11.1 ± 1.4	11.3 ± 1.4	>.20	>.20	>.20
Postoperative day 2	8.8 ± 1.2	9.8 ± 0.9	9.6 ± 1.1	.109	.244	>.20
Postoperative day 4 or discharge	9.5 ± 1.1	9.9 ± 0.9	9.5 ± 1.0	>.20	>.20	>.20
Platelet count (10 ³ cells/ μ L)						
Baseline	225 ± 66	204 ± 43	227 ± 53	>.20	>.20	>.20
After CPB (in operating room)	143 ± 53	148 ± 26	177 ± 42	>.20	.15	>.20
Postoperative day 2	130 ± 30	119 ± 28	143 ± 49	>.20	>.20	>.20
Postoperative day 4 or discharge	210 ± 57	173 ± 48	203 ± 62	>.20	>.20	>.20
Fibrinogen (mg/dL)						
Baseline	443 ± 56	384 ± 63	431 ± 115	>.20	>.20	>.20
After CPB (in operating room)	204 ± 61	209 ± 45	274 ± 52	>.20	.023	.038
International normalized ratio						
Baseline	1.0 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	>.20	>.20	>.20
After CPB	1.3 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	>.20	>.20	>.20
Prothrombin time (s)						
Baseline	11.0 ± 1.0	11.6 ± 1.6	10.7 ± 0.6	>.20	>.20	>.20
After CPB	14.0 ± 1.6	14.1 ± 1.6	12.8 ± 0.8	>.20	>.20	>.20
TEG						
Post-CPB r (mm)	12.3 ± 4.2	14.3 ± 5.5	12.1 ± 2.6	>.20	>.20	>.20
Post-CPB κ (mm)	4.0 ± 1.3	4.2 ± 0.8	2.9 ± 0.9	>.20	.09	.043
Post-CPB α (degrees)	66.9 ± 6.2	63.1 ± 5.2	72.8 ± 5.5	>.20	.152	.010
Post-CPB MA (mm)	57.8 ± 6.3	55.6 ± 3.5	64.3 ± 2.2	>.20	.016	.001

Data are mean $\pm$ SD. P values are based on ANOVA of data with Scheffé post hoc tests.

TABLE 5. Outcomes

Variable	Group I (n = 12)	Group II (n = 12)	Group III (n = 12)	P value
Intubation time in ICU (h, mean $\pm$ SD)	7.0 $\pm$ 6.7	7.0 $\pm$ 7.9	4.0 $\pm$ 2.4	>.20
Hospital stay (d, mean $\pm$ SD)	6.8 $\pm$ 4.3	5.2 $\pm$ 1.0	6.5 $\pm$ 2.8	>.20
Perioperative mortality (no.)	1 (8%)	0 (0%)	0 (0%)	>.20

The χ^2 test was used for categorical data; ANOVA was used for continuous variables.

was reduced by 8.4 U/mL with use of HBCs in group II versus group I ($P = .016$) 5 minutes into CPB, at which time the fibrinolytic response is known to rapidly increase. tPA was reduced even further, by 9.0 U/mL, with the elimination of cardiectomy suction in group III versus group I ($P = .003$) 5 minutes into CPB. No further measurements of tPA were performed, because its time course is known to peak during CPB and return to baseline after protamine reversal. PAI-1, on the other hand, is known to increase after protamine reversal, through the period in the ICU and postoperative day 1. PAI-1 was measured in a subset of patients ($n = 7$, $n = 7$, $n = 8$, groups I-III, respectively) and rose in all treatment groups by postoperative day 1. The large

variability in PAI-1 made it difficult to draw any conclusions, however, especially with the reduced sample size.

Inflammation (PMNE, IL-6, IL-8, and C5_{b-9}) was generally reduced with the addition of HBCs and further reduced with the elimination of cardiectomy suction (Table 7). Specifically, PMNE was reduced by 180 μ g/mL in group II versus group I ($P = .027$) and by 235 μ g/mL in group III versus group I ($P < .001$) at the post-CPB time point (Figure 2). Complement C5_{b-9} was reduced by 284 ng/mL in group III versus group I ($P = .026$) and by 284 ng/mL in group III versus group II ($P = .021$). C5_{b-9} levels had returned to baseline by 4 hours after CPB. IL-6 levels 4 hours after CPB were lower by 82 pg/mL in group II than in

Figure 1. Comparison of thrombin generation (PF-1.2) for different treatment strategies. *Diamonds*, Group I; *squares*, group II; *triangles*, group III. Asterisk indicates $P < .001$ for group I versus group III; plus sign indicates $P = .042$ for group II versus group III, by ANOVA and Scheffé test.

Figure 3. Comparison of platelet activation (β -TG) for different treatment strategies. *Diamonds*, Group I; *squares*, group II; *triangles*, group III. Asterisk indicates $P < .001$ for group I versus group III; plus sign indicates $P < .01$ for group I versus group II, by ANOVA and Scheffé test.

Figure 2. Comparison of PMNE for different treatment strategies. *Diamonds*, Group I; *squares*, group II; *triangles*, group III. Asterisk indicates $P < .001$ for group I versus group III; plus sign indicates $P = .027$ for group I versus group II, by ANOVA and Scheffé test.

group I ($P > .20$) and by 79 pg/mL in group III than group I ($P > .20$). Post-CPB IL-8 levels were lower by 7.7 pg/mL in group II than in group I ($P = .19$) and by 7.9 pg/mL in group III than in group I ($P = .18$). Despite these trends, the post-CPB IL-6 and IL-8 results did not reach statistical significance, perhaps because of the small sample size.

Platelet activation, as measured by β -TG and PF-4, was reduced immediately, 5 minutes into CPB, in groups III versus group I ($P < .001$) and remained lower at the post-CPB time point (Table 8). In particular, post-CPB β -TG was lower by 1779 IU/mL in group II than in group I ($P < .001$) and by 2046 IU/mL in group III than in group I ($P < .001$; Figure 3). Elimination of cardiomy suction

(group III vs group II) reduced post-CPB β -TG by a further 266 IU/mL ($P > .20$). Furthermore, platelet function, as measured by TEG, was also better preserved in group III (Table 4). Addition of heparin-bonded circuitry did not impart an effect on either of the neuronal injury markers, NSE nor S100 β (Figure 4). Elimination of cardiomy in group III, however, reduced NSE to baseline levels compared with both groups I and II ($P = .001$). Similarly, elimination of cardiomy reduced S100 β to baseline levels compared with group I ($P = .005$) and group II ($P < .05$).

Pairs of laboratory assay measurements were plotted against each other, and the plots showed approximate linear relationships. Post-CPB platelet activation markers, β -TG in particular, were strongly correlated with inflammation (PMNE; Figure 5). These markers also correlated significantly with thrombin ($r = 0.63$ and $r = 0.57$, respectively, $P < .01$).

Neurocognitive function (SDMT and RAVLT) at hospital discharge was better preserved (no deficits from baseline) in group III (Figures 6 and 7). Patients who were assessed at baseline (10/12 in group I, 11/12 in group II, and 9/12 in group III) were 80% to 100% compliant at discharge, depending on the test.

Discussion

This study was designed to assess and disassociate the independent effects of cardiomy suction and HBCs on systemic markers known to be elevated during and after CPB. These included thrombin generation (PF-1.2) platelet activation (PF-4, β -TG, and P-selectin) and fibrinolysis (tPA and PAI-1). In addition, the specific effects of cardiomy

Figure 4. A, Comparison of NSE for different treatment strategies. Diamonds, Group I; squares, group II; triangles, group III. Asterisk indicates $P < .001$ for group I versus group III; plus sign indicates $P < .001$ for group II versus group III, by ANOVA and Scheffé test. B, Comparison of S100 for different treatment strategies. Diamonds, Group I; squares, group II; triangles, group III. Asterisk indicates $P = .005$ for group I versus group III; plus sign indicates $P = .035$ for group II versus group III, by ANOVA and Scheffé test.

TABLE 6. Coagulation and fibrinolysis

	Group I (n = 12)		Group II (n = 12)		Group III (n = 12)		P value		
	Back-transformed $\log_{10}$ mean	$\log_{10}$ mean $\pm$ SEM	Back-transformed $\log_{10}$ mean	$\log_{10}$ mean $\pm$ SEM	Back-transformed $\log_{10}$ mean	$\log_{10}$ mean $\pm$ SEM	I vs II	I vs III	II vs III
PF-1.2 (nmol/L)									
Baseline	1.2	0.07 ± 0.07	1.3	0.10 ± 0.05	1.2	0.08 ± 0.055	$>.20$	$>.20$	$>.20$
5 min on CPB	1.5	0.18 ± 0.08	1.1	0.047 ± 0.051	1.1	0.025 ± 0.025	$>.20$	$>.20$	$>.20$
After CPB	5.0	0.70 ± 0.85	3.0	0.47 ± 0.093	1.5	0.19 ± 0.19	.12	$<.001$	.042
4 h after CPB	3.3	0.51 ± 0.50	2.2	0.35 ± 0.033	2.3	0.36 ± 0.36	.053	.058	$>.20$
tPA activity (U/mL)									
Baseline	0.2	-0.78 ± 0.16	0.6	-0.24 ± 0.10	0.4	-0.45 ± 0.17	.02	$>.20$	$>.20$
5 min on CPB	10.5	1.02 ± 0.22	2.1	0.33 ± 0.14	1.5	0.17 ± 0.08	.016	.003	$>.20$
After CPB	1.7	0.24 ± 0.16	1.7	0.22 ± 0.16	1.6	0.19 ± 0.17	$>.20$	$>.20$	$>.20$
PAI-1 activity (U/mL)									
Baseline	20.8	1.32 ± 0.09	6.6	0.82 ± 0.12	5.8	0.77 ± 0.23	.14	.08	$>.20$
5 min on CPB	1.2	0.08 ± 0.43	1.2	0.08 ± 0.41	2.5	0.39 ± 0.39	$>.20$	$>.20$	$>.20$
After CPB	11.8	1.07 ± 0.17	8.5	0.93 ± 0.22	2.6	0.42 ± 0.38	$>.20$	$>.20$	$>.20$
4 h after CPB	21.9	1.35 ± 0.46	46.8	1.68 ± 0.13	36.3	1.56 ± 0.23	$>.20$	$>.20$	$>.20$
Postoperative day 1	16.2	1.21 ± 0.64	63.2	1.80 ± 0.09	25.1	1.40 ± 0.11	$>.20$	$>.20$	$>.20$

P values are based on ANOVA of $\log_{10}$ data with Scheffé post hoc tests.

omy suction and HBCs on markers of inflammation (PMNE, C5_{b-9}, IL-6, and IL-8) and neuronal injury (NSE and S100 β) were assessed. Elevations in these markers had previously been attributed to CPB procedures themselves and to ischemia and reperfusion.

We hypothesized that expression of these markers can also be significantly influenced by technique (use or elimination of cardiomy suction), because cardiomy suction has been demonstrated to reintroduce particulate matter (fat emboli) as well as procoagulant and proinflammatory factors and debris from the surgical field, into the systemic

circulation.¹⁹⁻²³ These effects may blunt differences in outcomes related to CPB equipment.

The study has several limitations. Its power was chosen primarily to address effects of different therapies on markers of injury and was not sufficient to demonstrate major clinical differences. It was also designed to disassociate the effects of cardiomy suction from those of HBCs. The aim of the study was to define the effects of presence or absence of cardiomy suction when HBCs were used. Similarly, the aim was to define specific effects of non-HBCs versus HBCs when cardiomy suction was used. By design, how-

Figure 5. Correlation of post-CPB $\log_{10}$ PMNE and $\log_{10}$ β -TG. *Diamonds, Group I; squares, group II; triangles, group III; line, total population.* Pearson $r = 0.75$, $P < .01$.

Figure 6. Delayed memory, RAVLT VIII, by treatment group (box plots of difference scores). Score is based on asking patient to list as many of 15 words as are remembered after 20-minute break. $P = .126$ for group I versus group III, $P > .20$ for group II vs group III, by ANOVA and Scheffé test applied to difference scores.

ever, we did not specifically evaluate the effect of eliminating cardiomy suction in patients treated with non-HBCs; we did not attempt to make the assumption that the effect of eliminating cardiomy suction would be the same regardless of whether HBCs were used. Lower anticoagulation

Figure 7. Symbol discrimination, written SDMT, by treatment group (box plots of difference scores). $P = .054$ for group I versus group III, $P = .003$ for group II versus group III, by ANOVA and Scheffé test applied to difference scores.

(either through heparin or heparin-protamine complexes) may further lead to a decreased expression of inflammation, such as complement, neutrophil activation, interleukins, and other markers, which were decreased but not blunted in our patients treated with HBCs and kept at ACTs longer than 450 seconds. Finally, this study focused on patients undergoing isolated CABG with CPB. The relevance of these findings to patients undergoing cardiac procedures that require much more extensive cardiomy suction was not evaluated. Despite these limitations, the study was able to accomplish its stated objectives.

The findings of this study support our hypothesis that the use of cardiomy suction (particularly with non-HBC circuits) significantly increases post-CPB expression of markers for thrombin generation, inflammation, platelet activation, and neuronal injury. The use of HBCs, even when cardiomy suction was used, significantly blunted platelet activation and fibrinolysis. The use of HBCs with cardiomy suction, however, resulted in intermediate expression of markers for thrombin and inflammation but had no effect on elevation of markers of neuronal injury (NSE and S100 β). Finally, with elimination of cardiomy suction (group III), thrombin generation, PMNE, and neuronal injury markers were nearly completely blunted relative to groups I and II. Complement C5_{b-9} was significantly reduced in group III relative to groups I and II but not to baseline levels. The use of HBCs with or without cardiomy

TABLE 7. Inflammation

	Group I (n = 12)		Group II (n = 12)		Group III (n = 12)		P value		
	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	I vs II	I vs III	II vs III
PMNE 1.2 (μg/mL)									
Baseline	29.5	1.47 ± 0.103	36.3	1.56 ± 0.065	32.4	1.51 ± 0.048	>.20	>.20	>.20
5 min on CPB	55.0	1.75 ± 0.081	33.1	1.52 ± 0.075	26.3	1.41 ± 0.051	.084	.009	>.20
After CPB	307.1	2.49 ± 0.104	127.8	2.11 ± 0.093	74.6	1.87 ± 0.086	.027	<.001	>.20
4 h after CPB	114.8	2.06 ± 0.081	77.6	1.89 ± 0.039	46.8	1.67 ± 0.066	.2	.001	.07
Postoperative day 1	81.3	1.91 ± 0.124	77.6	1.89 ± 0.095	95.5	1.98 ± 0.12	>.20	>.20	>.20
IL-6 (pg/mL)									
Baseline	3.0	0.47 ± 0.11	3.1	0.49 ± 0.09	4.3	0.63 ± 0.11	>.20	>.20	>.20
5 min on CPB	4.2	0.62 ± 0.07	3.5	0.54 ± 0.09	5.4	0.73 ± 0.09	>.20	>.20	>.20
After CPB	67.6	1.83 ± 0.12	36.3	1.56 ± 0.09	33.1	1.52 ± 0.09	.16	.101	>.20
4 h after CPB	213.8	2.33 ± 0.07	131.8	2.12 ± 0.11	134.9	2.13 ± 0.08	>.20	>.20	>.20
IL-8 (pg/mL)									
Baseline	3.2	0.51 ± 0.06	3.6	0.56 ± 0.05	3.9	0.59 ± 0.10	>.20	>.20	>.20
5 min on CPB	4.1	0.61 ± 0.09	4.5	0.65 ± 0.07	4.2	0.62 ± 0.08	>.20	>.20	>.20
After CPB	16.2	1.21 ± 0.14	8.5	0.93 ± 0.07	8.3	0.92 ± 0.10	.19	.18	>.20
4 h after CPB	16.2	1.21 ± 0.10	11.0	1.04 ± 0.07	12.3	1.09 ± 0.08	>.20	>.20	>.20
Terminal complement									
C5 _{b-9} (ng/mL)									
Baseline	0.1	−0.99 ± 0.52	0.6	−0.25 ± 0.54	0.6	−0.25 ± 0.54	>.20	>.20	>.20
5 min on CPB	138.0	2.14 ± 0.42	354.8	2.55 ± 0.03	275.4	2.44 ± 0.08	>.20	>.20	>.20
After CPB	741.3	2.87 ± 0.05	741.3	2.87 ± 0.03	457.1	2.66 ± 0.07	>.20	.026	.021
4 h after CPB	0.4	−0.45 ± 0.82	0.21	−0.67 ± 0.58	0.74	−0.13 ± 0.57	>.20	>.20	>.20

P values are based on ANOVA of log₁₀ data with Scheffé post hoc tests.

omy suction diminished IL-6 and IL-8 levels in groups II and III relative to group I, but this difference did not reach statistical significance. The use of HBCs with or without cardiomy suction had no detectable effect on PAI-1 or P-selectin, although there was a trend toward reduced P-selectin at 4 hours after CPB in group III relative to groups I and II.

A significant correlation between markers of inflammation (PMNE) and platelet activation (β -TG, $r = 0.75$; Figure 5) as well as thrombin generation was also demonstrated. This suggests a possible common pathway or cross-activation.

Finally, we demonstrated that neurocognitive function, as measured by SDMT and RAVLT testing, was better preserved at discharge in group III.

The data from this study suggest that differences in the reported efficacy of HBCs for patients undergoing CABG may have been affected not only by differences in anticoagulation protocols (full vs lower) but by important differences in surgical technique (use of cardiomy suction), which may significantly abrogate the benefits conferred by HBCs. More important, the study challenges several commonly accepted precepts of cardiac surgery. One such notion is the belief that the use of cardiomy suction and open

systems, which are used ubiquitously (>90% of patients), is safe. This study supports previous studies¹⁹⁻²³ that demonstrated a deleterious effect of cardiomy suction and suggests that cardiomy suction use should be avoided whenever possible. This is relatively simple in CABG procedures because of minimal intraoperative mediastinal drainage (approximately 200 mL in this study). Use of cell saver techniques for these patients would not result in clinically significant loss of important components of whole blood and plasma. Further studies are necessary to develop effective strategies to blunt these deleterious effects when open systems and cardiomy suction are required (more invasive cardiac procedures).

Another commonly held precept is that CPB results in an obligatory, unalterable systemic insult. These data suggest that avoidance of cardiomy suction and the use of HBCs with a closed circuit (collapsible reservoir), elimination of blood-air interface, and defoaming agents can blunt many of these deleterious effects. Further pharmacologic approaches may be more effective once much of the perturbation has been significantly blunted to the levels achieved by this technique and equipment. Moreover, much of the current impetus for performing off-pump CABG is driven by the desire to avoid the perturbations in coagulation and inflam-

TABLE 8. Platelet activation

	Group I (n = 12)		Group II (n = 12)		Group III (n = 12)		P value		
	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	Back-transformed log ₁₀ mean	Log ₁₀ mean ± SEM	I vs II	I vs III	II vs III
PF-4 (IU/mL)									
Baseline	112.2	2.05 ± 0.12	117.5	2.07 ± 0.08	117.5	2.07 ± 0.11	>.20	>.20	>.20
5 min on CPB	169.8	2.23 ± 0.06	109.7	2.04 ± 0.04	72.4	1.86 ± 0.06	.059	<.001	.059
After CPB	380.2	2.58 ± 0.10	234.4	2.36 ± 0.05	141.3	2.15 ± 0.09	.19	.003	.19
4 h after CPB	162.2	2.21 ± 0.09	173.8	2.23 ± 0.071	144.5	2.16 ± 0.06	>.20	>.20	>.20
β-TG (IU/mL)									
Baseline	871	2.94 ± 0.11	691.8	2.84 ± 0.07	776.3	2.90 ± 0.12	>.20	>.20	>.20
5 min on CPB	1737.8	3.24 ± 0.15	478.6	2.68 ± 0.09	309.0	2.49 ± 0.07	.003	<.001	>.20
After CPB	2691.5	3.43 ± 0.07	912.0	2.96 ± 0.05	645.7	2.81 ± 0.10	<.001	<.001	>.20
4 h after CPB	1258.9	3.10 ± 0.11	1202.3	3.07 ± 0.08	955.0	3.0 ± 0.08	>.20	>.20	>.20
P-selectin (ng/mL)									
Baseline	36.3	1.56 ± 0.08	37.2	1.57 ± 0.06	45.7	1.67 ± 0.05	>.20	>.20	>.20
5 min on CPB	22.9	1.37 ± 0.07	22.9	1.37 ± 0.06	28.2	1.45 ± 0.05	>.20	>.20	>.20
After CPB	41.7	1.62 ± 0.07	32.4	1.51 ± 0.04	34.7	1.54 ± 0.06	>.20	>.20	>.20
4 h after CPB	63.1	1.80 ± 0.13	40.7	1.61 ± 0.04	38.9	1.59 ± 0.06	>.20	>.20	>.20

P values are based on ANOVA of log₁₀ data with Scheffé post hoc tests.

mation and the neuropsychologic injuries that are associated with CPB. In the absence of large, prospective, randomized trials, our data suggest that many of the deleterious effects previously attributed to CPB can be avoided when cardiomy suction is eliminated and HBCs are used. The significant elevation in markers of neuronal injury associated with on-pump CABG, and avoided by off-pump CABG, were blunted in this study, suggesting a better standard for future comparisons with off-pump CABG.

It is probable that significant elevations in NSE and S100β seen in patients treated with cardiomy suction do not represent direct cerebral injury but rather extracerebral sources, such as pump trauma (fat or ruptured platelets and red blood cells).²⁵⁻³⁶ This is supported by our data, which demonstrated no significant differences between groups or from baseline levels by the first postoperative day. Expression of these markers, regardless of their specific source, although not clearly representing direct causality, is associated with deleterious outcomes and deficits in neurocognitive function.

In summary, elimination of cardiomy suction was easy to effect for patients undergoing CABG and resulted in a minimal increase in cell saver blood. The combination of HBCs with elimination of cardiomy suction blunted many of the deleterious effects of CPB on markers of coagulation, inflammation, and neuronal injury and should be used whenever possible to enhance clinical outcomes. Future research is needed to further elucidate these mechanisms.

We acknowledge the following who assisted in the study: Jean Blue, RN, MN, ARNP, Victor Chan, MD, Scott Burks, MD, Joseph Lu, MD, Jan Fisher, Seema Nakravar, Ruth Degroot, Jean

Bergman, Sonja Borthen, RN, and Judith Folks, Northwest Hospital; Angela Farr, Joanne Estergren, Shannon Brown, Jacquie Chee, Sue Newman, Joanne Lloyd, Rick McMinn, and Janet Hollander, University of Washington Laboratories; Rolando Alberto, CCP, David Anderson, CCP, Arnold Benak, CCP, Jeff Dunn, CCP, Barbara Eisenstein, CCP, Gina Lindley, CCP, and Pam Williams, CCP, perfusionists; George B. McDonald, MD, Richard Lawler, Fred Hutchinson Cancer Research Center Cytokine Laboratory; and Brenda Townes, PhD, Peter Slade, PhD, and Gail Rosenbaum, Harborview Medical Center.

References

1. Videm V, Svennevig JL, Fosse E, Semb G, Osterud A, Mollnes TE. Reduced complement activation with heparin-coated oxygenator and tubings in coronary bypass operations. *J Thorac Cardiovasc Surg.* 1992;103:806-13.
2. Pekna M, Hagman L, Halden E, Nilsson UR, Nilsson B, Thelin S. Complement activation during cardiopulmonary bypass: effects of immobilized heparin. *Ann Thorac Surg.* 1994;58:421-4.
3. Fosse E, Moen O, Johnson E, Semb G, Brockmeier V, Mollnes TE, et al. Reduced complement and granulocyte activation with heparin-coated cardiopulmonary bypass. *Ann Thorac Surg.* 1994;58:472-7.
4. Ovrum E, Mollnes TE, Fosse E, Holen EA, Tangen G, Ringdal ML, et al. High and low heparin dose with heparin-coated cardiopulmonary bypass circuits: activation of complement and granulocytes. *Ann Thorac Surg.* 1995;60:1755-61.
5. Videm V, Mollnes TE, Bergh K, Fosse E, Moht B, Hagve T, et al. Heparin-coated cardiopulmonary bypass equipment. II: Mechanisms for reduced complement activation in vivo. *J Thorac Cardiovasc Surg.* 1999;117:803-9.
6. Gu YJ, Oeveren W, Akkerman C, Boonstra PW, Huyzen RJ, Wildevuur CR. Heparin-coated circuits reduce the inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg.* 1993;55:917-22.
7. Spiess BD, Vocelka C, Cochran RP, Soltow L, Chandler WL. Heparin coated bypass circuits (Carmeda) suppresses the release of tissue

- plasminogen activator during coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth*. 1998;12:299-304.
8. Edmunds LH. Surface-bound heparin—panacea or peril? *Ann Thorac Surg*. 1994;58:285-6.
 9. Aldea GS, Doursounian M, O’Gara P, Treanor P, Shapira OM, Lazar HL, et al. Heparin-bonded cardiopulmonary bypass circuits and a reduced anticoagulation protocol in patients undergoing primary CABG: a prospective randomized study. *Ann Thorac Surg*. 1996;62:410-8.
 10. Aldea GS, O’Gara P, Shapira OM, Treanor P, Osman A, Patalis E, et al. Effect of anticoagulation protocol on outcome in patients undergoing CABG with heparin-bonded cardiopulmonary bypass circuits. *Ann Thorac Surg*. 1998;65:425-33.
 11. Borowiec J, Thelin S, Bagge L, Hultman J, Hansson H. Decreased blood loss after cardiopulmonary bypass using heparin-coated circuit and 50% reduction of heparin dose. *Scand J Thorac Cardiovasc Surg*. 1992;26:177-85.
 12. Boonstra PW, Gu YJ, Akkerman C, Haan J, Huyzen R, van Oeveren W. Heparin coating of an extracorporeal circuit partly improves hemostasis after cardiopulmonary bypass. *J Thorac Cardiovasc Surg*. 1994;107:289-92.
 13. Shapira OM, Aldea GS, Zelingher J, Volpe C, Fitzgerald C, DeAndrade K. Enhanced blood conservation and improved clinical outcome after valve surgery using heparin-bonded cardiopulmonary bypass circuits. *J Card Surg*. 1996;11:307-17.
 14. Aldea GS, Shemin RJ. Heparin-bonded circuits improve clinical outcomes in patients undergoing CABG: a new “gold” standard? *Am Coll Cardiol Curr J Rev*. 1998;7:45-50.
 15. Ranucci M, Cirri S, Conti D, Ditta A, Boncilli A, Frigiola A, et al. Beneficial effects of Duraflow II heparin-coated circuits on postperfusion lung dysfunction. *Ann Thorac Surg*. 1997;61:76-81.
 16. Ranucci M, Mazzucco A, Pessotto R, Grillone G, Casati V, Porreca L, et al. Heparin-coated circuits for high-risk patients: a multicenter prospective randomized trial. *Ann Thorac Surg*. 1999;67:994-1000.
 17. McCarthy PM, Yared JP, Foster RC, Ogella DA, Borsh JA, Cosgrove DM. A prospective randomized trial of Duraflow II heparin-coated circuits in cardiac reoperations. *Ann Thorac Surg*. 1999;67:1268-73.
 18. Brooker RF, Brown WR, Moody DM, Hammon JW, Reboussin DM, Deal DD, et al. Cardiomyotomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg*. 1998;65:1651-5.
 19. Reents W, Babin-Ebell J, Misoph MR, Schwarzkopf A, Elert O. Influence of different autotransfusion devices on the quality of salvaged blood. *Ann Thorac Surg*. 1999;68:58-62.
 20. Phillippou H, Adami A, Davidson SJ, Pepper SJ, Burman JF, Lane DA. Tissue factor is rapidly elevated in plasma collected from the pericardial cavity during cardiopulmonary bypass. *Thromb Haemost*. 2000;84:124-8.
 21. Andersen RE, Hansson LO, Liska J, Settergren G, Vaage J. The effect of cardiomyotomy suction on brain injury markers and S100 β after cardiopulmonary bypass. *Ann Thorac Surg*. 2000;69:847-50.
 22. Johnsson P, Blomquist S, Luhrs C, Malmkvist G, Alling C, Solem J, et al. Neuron-specific enolase increase in plasma during and immediately after extracorporeal circulation. *Ann Thorac Surg*. 2000;69:750-4.
 23. Borowiec JW, Bozdayi M, Jaramillo A, Nilsson L, Venge P, Henze A. Influence of two blood conservation techniques (cardiomyotomy reservoir versus cell saver) on biocompatibility of heparin coated cardiopulmonary bypass during coronary revascularization surgery. *J Card Surg*. 1997;12:190-7.
 24. Davila-Romain VG, Barzilai B, Wareing TH, Murphy SF, Schechtman KB, Kouhoukos NT. Atherosclerosis of the ascending aorta: prevalence and role as an independent predictor of cerebrovascular events in cardiac patients. *Stroke*. 1994;25:2010-6.
 25. Johnsson P, Johnsson P, Alling C, Westaby S, Blomquist S. Significance of serum S100 release after coronary artery bypass grafting. *Ann Thorac Surg*. 1998;65:1639-44.
 26. Grocott HP, Croughwell ND, Amory DW, White WD, Kirchner JL, Newman MF. Cerebral emboli and serum S100 β during cardiac operations. *Ann Thorac Surg*. 1998;65:1645-50.
 27. Gill R, Murkin JM. Neuropsychologic dysfunction after cardiac surgery: what is the problem? *J Cardiothorac Vasc Anesth*. 1996;10:91-8.
 28. Borowicz LM, Goldsborough MA, Selnes OA, McKhann GM. Neuropsychologic change after cardiac surgery: a clinical review. *J Cardiothorac Vasc Anesth*. 1996;100:105-12.
 29. Mahana EP, Blumenthal JA, White WD, Croughwell ND, Clancy CP, Smith R, et al. Defining neuropsychological dysfunction after coronary artery bypass grafting. *Ann Thorac Surg*. 1996;61:1342-47.
 30. Barone FC, Clark RK, Price WJ, White RF, Feuerstein GZ, Storer BL, et al. Neuron-specific enolase increases in cerebral and systemic circulation following focal ischemia. *Brain Res*. 1993;623:77-82.
 31. Cooper EH. Neuron-specific enolase. *Int J Biol Markers*. 1994;9:205-10.
 32. Johnsson P, Lundqvist C, Lindgren A, Ferencz I, Alling C, Stahl E. Cerebral complications after cardiac surgery assessed by S-100 and NSE levels in blood. *J Cardiothorac Vasc Anesth*. 1995;9:694-9.
 33. Taggart DP, Bhattacharya K, Meston N, Standing SJ, Kay JD, Pillai R, et al. Serum S-100 protein concentration after cardiac surgery: a randomized trial of arterial line filtration. *Eur J Cardiothorac Surg*. 1997;11:645-9.
 34. Jonsson H, Johnsson P, Alling C, Backstrom M, Bergh C, Blomquist S. S-100 β after coronary artery surgery: release pattern, source of contamination and relation to neuropsychological outcome. *Ann Thorac Surg*. 1999;68:2202-8.
 35. Anderson RE, Hansson LO, Nilsson O, Liska J, Settergren G, Vaage J. Increase in serum S100A1-B and S100BB during cardiac surgery arises from extracerebral sources. *Ann Thorac Surg*. 2001;71:1512-7.
 36. Jonsson H, Johnsson P, Birch-Jensen M, Alling C, Westaby S, Blomquist S. S100B as a predictor of size and outcome of stroke after cardiac surgery. *Ann Thorac Surg*. 2001;71:1433-7.

Discussion

Dr Andrew S. Wechsler (Philadelphia, Pa). Aldea and colleagues appear to have demonstrated that the use of HBCs in the CPB system diminishes activation of inflammatory markers, diminishes the coagulation and lytic response to bypass, diminishes white blood cell and platelet activation, and may provide some clinical benefit. Avoidance of cardiomyotomy suction further enhanced the benefit accrued by the use of HBCs. I have a few observations and questions.

First, your patient population was carefully selected, cross-clamp times were short, and CPB times were short. One could argue that the differences between groups that were observed would be enhanced in the setting of more complex operations.

Alternatively, if the stimulus were great enough, the differences observed might be obscured by greater activation of inflammatory and coagulation markers. What do you think?

Dr Aldea. I think that the former is possible. In fact, there are two patient populations that we look at. One is a CABG population. Typically the amount of cardiomyotomy suction is rather limited in volume, as I have shown here, so there is a potential that in more complex intracardiac procedures the much more extensive blood-air interaction and greater cardiomyotomy volume would lead to more inflammation. These effects would be accentuated. We are in the process of designing a study to look at these differences, and I think that this comment is correct. We expect that there will be

much more accentuated effects in settings when cardiomy suction and blood-air interfaces are increased.

Dr Wechsler. Second, your studies were performed at “moderate systemic hypothermia.” This is a somewhat vague term, and it would be important to know the perfusate temperature during CPB. Do you agree that hypothermia appears to exacerbate the inflammatory and thrombotic cascade?

Dr Aldea. What we did in this particular study and in our previous studies is what we term “near-normothermia,” that is, that there is no active cooling. Typically the patient’s temperature drifts to approximately 35°. In fact, if it drifts below that we actively start rewarming. There is no question that there is an effect of hypothermia on coagulation, with accentuated coagulopathy. I am not sure what the effect would be on inflammatory changes. In this particular study we controlled for the temperature, so I think that the effects are predominantly related to the elimination of cardiomy.

Dr Wechsler. I am a little concerned about one aspect of your experimental design. Why did you not keep the cardiomy reservoir constant across all groups? Is it possible that using a collapsible heparin-bonded reservoir in the HBC group without cardiomy suction might have contributed to the diminution of inflammation and coagulation disorders relative to the hard-shell heparin-coated reservoir used for the patients who had cardiomy suction? By using two different reservoirs, have you potentially obviated the difference between cardiomy suction and incriminated the type of reservoir? The blood-air interface may be as important as the suction per se.

Dr Aldea. That is a good question. My impression in having measured some of the contents of cardiomy suction is that there is an independent effect of blood-air interaction that could potentially increase coagulation abnormalities. However, the effect of particulate matter was shown by Stump’s work demonstrating an increasing number of cerebral emboli, which are probably related to fat embolization and other particulate matter from the wound not filtered by arterial filters. This effect, as well as other procoagulant and proinflammatory factors, are independent of the physical shape of the reservoir itself. I think that the effects are real, and I do recognize that there was an issue with that. We have tried to correct for it as much as possible.

Dr Wechsler. You apparently used two different oxygenators, one in the non-HBC group and one in the HBC groups. Could this have contributed to some of the observed differences?

Dr Aldea. Again, the main differences we believe are due to the cardiomy suction, and the reason we can support this is the differences we measured with the cardiomy suction per se. Those were the oxygenators available to us. There was only a small variation between them related to the configuration of the non-HBC system that was available to us for the purpose of the study.

Dr Wechsler. Your study was designed thoughtfully, with careful power calculations to determine differences noted between inflammatory and thrombotic markers. However, in your analysis you attempted to correlate isolated clinical variables with these measurements, specifically lung compliance and transfusion units. The correlation coefficients are not particularly convincing, and I wonder whether you have gone further with your data than is actually justified. For such a comparison to be valid, one would

have to use a protocol that included specific transfusion triggers, which were not specified in your article.

Dr Aldea. We did have specific transfusion triggers and a protocol in place, and all transfusion was triggered by clinical pathways and TEG, as well as actual amount of bleeding, so that was accounted for. I think that the criticism that the study was not designed to look at clinical end points but rather at laboratory markers is correct. The study was designed on the basis of previous data that demonstrated that with the use of HBCs we can decrease the expression of these laboratory markers by approximately 50%. We were, however, surprised that despite this we could make some associations with clinical end points and just wanted to emphasize the point that these markers are not of just biochemical interest but are of some clinical relevance.

Dr Wechsler. Some investigators have demonstrated that protein coating of bypass circuits is equally effective in minimizing adverse markers associated with CPB. Do you believe that heparin plays a unique role in the answer, could the answer be found in other natural or synthetic surface coatings?

Dr Aldea. This is a difficult question to answer. I think you have to test each individual circuit. I think that it is problematic to take a concept that the coatings themselves, which within minutes are coated by secondary protein layers, have similar properties. We know that different coatings may exert different properties. We know that some coatings protect from platelet dysfunction but do not necessarily diminish the inflammatory response to CPB, so I think that this is a problematic area. When new products are introduced, I believe that they must be rigorously tested to make sure that in fact they have the same efficacy as the well-tested circuits that exist now and have withstood the scrutiny of a large clinical experience.

Dr Wechsler. Could you comment as to whether any of the data were accrued in a blinded fashion? I would assume that this was the case for all the laboratory data but not the case for the clinical data. Is this correct?

Dr Aldea. All the surgeons were blinded to treatment group at the time of surgery, and the caregivers were blinded afterward.

Dr Wechsler. These questions were designed to stimulate some discussion and not to detract from the quality of this excellent study. I commend you and your colleagues for attempting to sort out those factors most responsible for the adverse events associated with CPB that may be influenced by heparin bonding or procedural strategies.

Dr Gregory Misbach (*San Bernadino, Calif*). Can you give us any hints on how best to minimize cardiomy suction in a variety of cases, including for instance valve operations? Are there any particular strategies that you would recommend to help us receive the benefits of what you are showing us today?

Dr Aldea. This study was designed primarily to look at the CABG population, and again if you look at this moment at clinical practice in the United States more than 95% of centers are using routine cardiomy suction when CPB is used during CABG. What we have shown is that in fact the amount of fluid that you get when you use cardiomy suction during routine CABG, even a reoperation, is quite small, whereas the detrimental effects are significant. I think that one has to rethink and redesign cardiomy

suction if these effects can be demonstrated for patients undergoing more invasive cardiac procedures, such as valve replacement. There are two implications. First, we might have to change the filtration system. Second, I think that the biggest variable is the stagnant pericardial blood. It may be that because in valve proce-

dures you do not have the stagnation and the active biologic surfaces of the pericardium to deal with, the results may be different. The relevance of the application of this concept to pediatric cases and intracardiac cases has to be carefully looked at.

Availability of Journal back issues

As a service to our subscribers, copies of back issues of *The Journal of Thoracic and Cardiovascular Surgery* for the preceding 5 years are maintained and are available for purchase from Mosby until inventory is depleted. Please write to Mosby, Subscription Customer Service, 6277 Sea Harbor Dr, Orlando, FL 32877, or call 800-654-2452 or 407-345-4000 for information on availability of particular issues and prices.