Coronary artery bypass surgery with heparin-coated perfusion circuits and low-dose heparinization

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Objective: To evaluate the safety and efficacy of heparin-coated perfusion circuits with low-dose heparinization and centrifugal pumping compared with the standard method during coronary artery bypass grafting. **Design:** Prospective, randomized, single-blind clinical trial. **Setting:** A primary care institution. **Patients:** Ninety patients who underwent first-time elective coronary artery bypass grafting were eligible for the study. After giving informed consent, they were randomly assigned to 1 of 3 groups (30/group). **Interventions:** Perfusion on regular uncoated bypass equipment with a roller pump and full-dose heparinization (300 IU/kg bolus, activated clotting time [ACT] > 400 s) (group 1), on a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization (group 2) and on fully heparin-coated bypass equipment with a centrifugal pump and low-dose heparinization (100 IU/kg bolus, ACT of 180–400 s) (group 3). Standard coronary artery bypass grafting was performed. **Outcome measures:** Postoperative bleeding, transfusion requirements and clinical outcomes. **Results:** There were no complications related to the study protocol. Study groups were similar in terms of postoperative bleeding, transfusion requirements and clinical outcomes. **Conclusions:** Heparin-coated cardiopulmonary bypass with low-dose heparinization and centrifugal pumping is a safe practice but showed no advantages over the use of regular uncoated bypass circuits for coronary bypass surgery.

Objectif : Évaluer, au cours d'un pontage aortocoronarien, l'innocuité et l'efficacité des circuits de perfusion enduits d'héparine avec héparinisation à faible dose et pompe centrifuge, par rapport à celles de la méthode usuelle. **Conception :** Étude clinique prospective randomisée à simple insu. **Contexte :** Établissement de soins primaires. **Patients :** Quatre-vingt-dix patients ayant subi pour la première fois un pontage aortocoronarien électif étaient admissibles à l'étude. Après avoir donné leur consentement éclairé, ils ont été répartis au hasard en trois groupes (30 patients par groupe). **Interventions :** Perfusion au moyen de l'équipement non enduit régulier avec pompe à galet et héparinisation par dose complète (bolus de 300 UI/kg, temps de coagulation activée [TCA] > 400 secondes) (groupe 1), au moyen d'un oxygénateur enduit d'héparine avec pompe centrifuge et héparinisation par dose complète (groupe 2) et au moyen d'un équipement entièrement enduit d'héparine avec pompe centrifuge et héparinisation à faible dose (bolus de 100 UI/kg, TCA de 180 à 400 secondes) (groupe 3). Un pontage aortocoronarien type a été pratiqué. **Mesures de résultats :** Saignement postopératoire, transfusions requises et résultats cliniques. **Résultats :** Il n'y a pas eu de complications associées au protocole de l'étude. Les groupes de l'étude se ressemblaient pour ce qui est du saignement postopératoire, des transfusions requises et des résultats cliniques. **Conclusions :** La circulation extracorporelle avec enduit d'héparine, qui fait appel à une héparinisation à faible dose à l'aide d'une pompe centrifuge, est une intervention sans danger, mais elle n'a pas présenté d'avantages par rapport à l'utilisation des circuits de perfusion non enduits réguliers dans le pontage aortocoronarien.

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Presented at the 52nd annual meeting of the Canadian Cardiovascular Society, Québec City, Québec, October 1999.

Accepted for publication July 13, 2001.

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Cardiopulmonary bypass (CPB) involves exposure of blood to foreign surfaces. Clotting is avoided by administering heparin at high doses; however, the more insidious consequences of inflammatory activation proceed unchecked, leading to varying degrees of multiple-organ dysfunction known as the "post-perfusion syndrome." Systemic heparinization also carries the risks of increased postoperative bleeding and need for transfusion. A heparin-coated contact surface might provide a more biocompatible environment and allow for low-dose heparinization.

Roller pumps are the standard modality for driving blood though the CPB circuit. This may cause blood-cell trauma, resulting in hemolysis, platelet depletion and an inflammatory reaction. A centrifugal pump might lessen these effects.

We performed a randomized clinical trial of heparin-coated CPB with low-dose heparinization and centrifugal pumping in patients who underwent elective coronary artery bypass grafting (CABG) to determine whether the equipment is superior with respect to postoperative bleeding and clinical outcomes.

Methods

Patient population

Patients scheduled to undergo elective CABG were eligible for the study. Exclusion criteria were reoperation, emergent surgery, age older than 80 years, weight less than 50 kg, a left ventricular ejection fraction less than 35%, congestive heart failure, severe pulmonary disease, known coagulopathies or other conditions suspected to affect transfusion requirements, and the need for ongoing anticoagulation. Informed consent was obtained from patients before their inclusion in the study. Ninety patients were entered into the study.

Randomization and study groups

Patients were randomly assigned to 1 of 3 groups (30 patients each). Group 1 was the control and comprised patients perfused on regular uncoated bypass equipment with a roller pump and full-dose heparinization (300 IU/kg bolus, activated clotting time [ACT] > 400 s). Group 2 patients were perfused on a heparin-coated oxygenator (Carmeda; Medtronic, Minneapolis, Minn.) with a centrifugal pump (Medtronic Biomedicus, Eden Prairie, Minn.) and full-dose heparinization. Group 3 patients were perfused on fully heparin-coated bypass equipment (Carmeda; Medtronic) with a centrifugal pump and low-dose heparinization (100 IU/kg bolus, ACT of 180–400 s).

Intraoperative management

Patients underwent standard CABG. CPB was initiated as indicated by study group. An additional 10 000 IU of heparin was included in the pump priming solution. Cardiac arrest was achieved and maintained via antegrade, intermittent, cold blood cardioplegia and adjunctive cold topical saline.

Postoperative management and follow-up

Postoperatively, patients received transfusions of red cells, fresh frozen plasma, platelets or cryoprecipitate according to a predetermined protocol (Appendix 1). Chest tubes were connected to 20 mm Hg suction and were removed when drainage was less than 100 mL every 8 hours. Patients were extubated when their ventilatory parameters met standardized criteria (Appendix 2). They were usually discharged on the fifth postoperative day.

Hematologic and biochemical data were measured preoperatively, 5 minutes after cross-clamp release, 20 minutes after discontinuation of CPB, on arrival in the intensive care unit and on the morning of the first postoperative day. Tumour necrosis factor (TNF) was assayed with the Biotrak TNF-α, human ELISA system code RPN 2148 (Amersham International, Little Chalfort, Bucks, UK). Patients were followed-up until hospital discharge.

Statistics

Statistical analysis was performed using SPSS software (SPSS, Chicago, Ill.). Continuous variables were compared among groups using 1-way analysis of variance and Kruskal–Wallis tests where nonparametric analysis was indicated. Discrete variables were compared among groups using Fisher's exact and χ^2 tests where appropriate. Results are expressed as the mean (and standard error of the mean). A probability value of 0.05 or less was considered significant.

Ethics

This study was approved by the University of Alberta Faculty of Medicine Research Ethics Board and was conducted within the guidelines of the board.

Results

Four patients from group 3 had intraoperative protocol deviations and were excluded from analysis, leaving 86 patients in the trial: 3 patients received full-dose heparinization and 1 had a suspected clot in the operative field. Three patients required reoperation for surgical bleeding (2 in group 1 and 1 in group 3), and their postoperative data were therefore excluded. Postoperative results were excluded for 1 patient in group 3 who died secondary to aspiration pneumonia, which began on postoperative day 3.

Patient demographics are summarized in Table 1. There were no significant differences among groups. Hematologic and biochemical findings were also similar among groups (Table 2). Fig. 1 illustrates the similar changes in hemoglobin in each group. Hourly chest tube drainage is

depicted in Fig. 2. There was no significant difference among groups. Fig. 3 shows TNF levels at each time point. Group 2 had a greater TNF level than groups 1 and 3 on arrival in the intensive care unit, and group 1 had a greater postoperative day 1 TNF level than group 3. Medications administered are presented in Table 3, intraoperative variables are summarized in Table 4, postoperative transfusion requirements are presented in Fig. 4, and Table 5 summarizes the remaining postoperative variables and outcomes. There were no complications related to the study protocol.

Discussion

Heparin coating

CPB involves exposure of blood to foreign surfaces with consequent activation of humoral and cellular defence mechanisms leading to a whole-body inflammatory response. Unaltered, the immediate consequence of activation would be widespread coagulation with clotting of the bypass equipment and thromboembolism. Presently this is avoided with high-dose heparin, which disarms the coagulation cascade. Although clotting is avoided, the more insidious consequences of inflammatory activation proceed unchecked, leading to varying degrees of the postperfusion syndrome. A more biocompatible blood contact surface would theoretically lessen the morbidity and occasional mortality attendant upon activation of these host defences. As well, high-dose systemic heparinization carries the risk of increased postoperative bleeding and transfusion requirements. Application of a heparin-coated CPB circuit allows a significant reduction in systemic heparinization.

Table 1

Demographics for Patients Who Underwent Coronary Artery Bypass Grafting in the Three Groups

Feature	Group* 1 (*n* = 30)	2 (*n* = 30)	3 (*n* = 26)	Overall (*n* = 86)	*p* value
Mean (and SEM) age, yr	64 (1)	61 (2)	63 (1)	62 (1)	0.34
Sex, M/F	26/4	26/4	23/3	75/11	0.97
Mean (and SEM) weight, kg	83.1 (2.4)	91.8 (3.7)	87.9 (3.1)	87.6 (1.8)	0.27
Mean (and SEM) body mass index, kg/m≤	28.5 (0.7)	30.7 (1.0)	29.1 (1.0)	29.4 (0.5)	0.41
Hypertension, no. (and %)	19 (63)	20 (67)	15 (58)	54 (63)	0.78
Diabetes mellitus, no. (and %)	7 (23)	10 (33)	5 (19)	22 (26)	0.45
Myocardial infarction, no. (and %)	12 (40)	14 (47)	13 (50)	39 (45)	0.74
Mean (and SEM) no. of diseased vessels	3 (1)	3 (1)	3 (1)	3 (1)	0.17
Renal dysfunction,† no. (and %)	1 (3)	0	2 (8)	3 (3)	0.29
Mean (and SEM) ejection fraction, %	51 (2)	55 (2)	49 (2)	52 (1)	0.07

*1 = patients perfused on uncoated bypass equipment with a roller pump and full dose systemic heparinization, 2 = patients perfused on a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization, 3 = patients perfused on fully heparin-coated bypass equipment with a centrifugal pump and low-dose systemic heparinization.
†Renal dysfunction = creatinine > 200 µmol/L

Table 2

Hematologic and Biochemical Measurements (Mean (and SEM)) at Three Measurement Times* for Patients Who Underwent Coronary Artery Bypass Grafting

Measurement	Group 1 (*n* = 30)	2 (*n* = 30)	3 (*n* = 26)	Overall (*n* = 86)	*p* value
Platelet count, $\times 10^9$/L					
Preop	230 (13)	203 (8)	208 (13)	214 (7)	0.22
ICU	133 (8)	116 (8)	129 (9)	126 (5)	0.13
Postop day 1†	164 (8)	153 (8)	150 (9)	156 (5)	0.48
Leukocyte count, $\times 10^9$/L					
Preop	6.7 (0.3)	6.8 (0.3)	6.6 (0.4)	6.7 (0.2)	0.49
Postop day 1†3	12.3 (0.5)	12.0 (0.6)	11.6 (0.8)	12.0 (0.4)	0.79
Creatinine, µmol/L					
Preop	102 (4)	101 (3)	101 (6)	101 (2)	0.58
Postop day 1†	94 (4)	97 (3)	94 (6)	95 (3)	0.42
Prothrombin time, INR					
Preop	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.26
ICU	1.3 (0.1)	1.2 (0.1)	1.2 (0.1)	1.2 (0.1)	0.69
Partial thromboplastin time, s					
Preop	40 (3)	36 (3)	38 (3)	38 (2)	0.45
ICU	36 (1)	35 (2)	35 (2)	36 (1)	0.43

*Preoperatively (preop), on arrival in the intensive care unit (ICU) and on the morning of postoperative day 1 (postop)
INR = international normalized ratio.
†Group 1, *n* = 28; group 2, *n* = 30; group 3, *n* = 25; overall, *n* = 83.

There have been a number of recent investigations into the use of heparin-coated circuits.[1–19] Such circuits have not been shown to reduce postoperative mortality,[1–7] improve postoperative kidney function,[1,4,8] alter postoperative hemodynamics,[9] or affect postoperative fluid balance.[9] Some investigators have found that heparin-coated circuits are beneficial in terms of postoperative morbidity,[10,11] whereas others have not.[1–5,7] The need for ventilator support has been reduced with this technique in some studies[12–14] and unaffected in others.[1,2,8,9,11] Similarly, some authors have reported shortened intensive care unit[10,11,14] and hospital stays,[10,12,14] whereas others have not.[2,3] Inotropic support requirements have been both reduced[10] and unaffected[4] by this technique. Authors generally agree that the circuit is completely safe compared to the standard.[1–18]

Our results show no significant difference among the study groups in the following postoperative variables: serum creatinine, leukocyte count, inotrope or vasodilator administration, mechanical assistance, pacing, 24-hour fluid balance, postoperative weight gain, respiratory failure, coagulopathy, reoperation for bleeding, organ failure, mortality, intubation time, length of stay in the intensive care unit and inhospital. TNF levels were significantly greater for group 2 on arrival in the intensive care unit and for group 1 on postoperative day 1. The low absolute levels of TNF, however, are insignificant, and these differences are likely statistical artifacts.

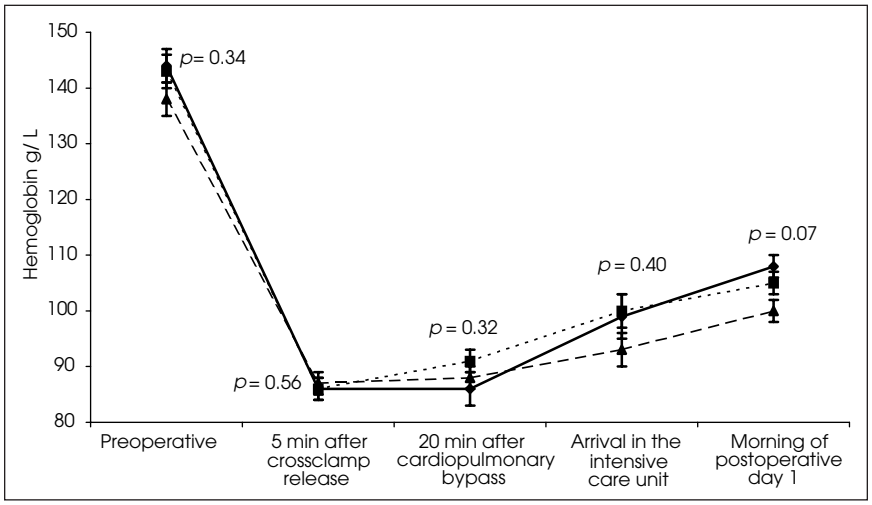

FIG. 1. Hemoglobin changes in patients undergoing coronary artery bypass grafting using regular uncoated bypass equipment with roller pump and full-dose heparinization (group 1, diamonds), a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization (group 2, squares) or fully heparin-coated bypass equipment with a centrifugal pump and low-dose heparinization (group 3, triangles).

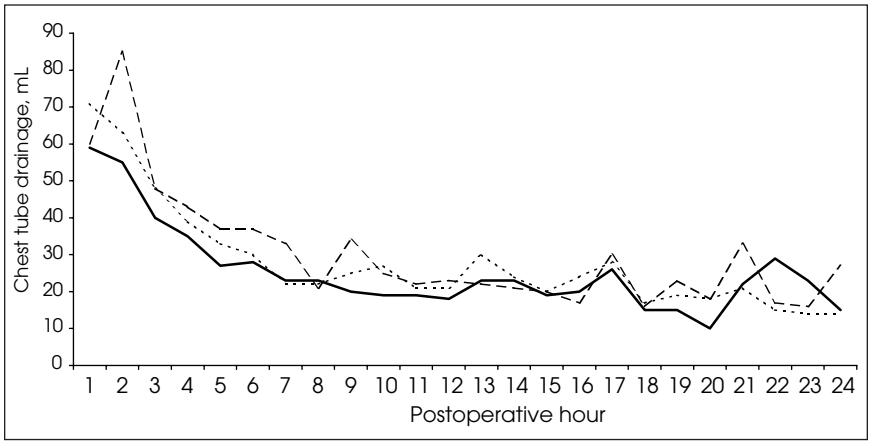

FIG. 2. Postoperative chest tube drainage in patients undergoing coronary artery bypass grafting using regular uncoated bypass equipment with roller pump and full-dose heparinization (group 1, solid line), a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization (group 2, dotted line) or fully heparin-coated bypass equipment with a centrifugal pump and low-dose heparinization (group 3, dashed line).

TNF is a powerful inflammatory mediator[20,21] that has previously been considered a very useful indicator of post-CPB morbidity.[22] Studies examining the inflammatory response in patients undergoing CABG found TNF levels significantly increased after aortic cross-clamp release, peaking 30 minutes after bypass.[22,23] Heparin coating of perfusion circuits has been shown to markedly reduce TNF production after CPB.[15,18] Other trials, however, have failed to detect TNF after standard CPB.[13,16,24] This has led some investigators to question the value of TNF as an indicator of the post-perfusion syndrome; thus, our results with TNF should be interpreted with caution.

Low-dose heparin

The systemic administration of high-dose heparin carries the inherent risks of postoperative bleeding and need for transfusions. Heparin coating of the perfusion circuit allows for low-dose heparin administration during CPB.

The use of low-dose systemic heparinization in conjunction with heparin-coated circuits has been explored in a number of studies. Findings have varied substantially. Most trials have shown that 24-hour chest tube drainage is reduced,[6,7,10,12,17] whereas some have not.[1,3] Hemoglobin preservation and reduced bleeding has been seen in some studies[1,5] but not in others.[3,4,19] Similarly, postoperative hematocrit levels have been improved in some trials[5,17] but not all.[6,12] No benefits have been demon-

strated in postoperative platelet numbers[1,3,4] or function.[4] Studies have demonstrated a reduction in the volumes of red cells,[6,7,10,17] plasma[7] and platelets[7] transfused, as well as total transfusions[5,7,12] and the likelihood of requiring a transfusion.[5,7,10] Others, including our own, have shown no reduction in transfusion requirements.[1,3,4,19] Reoperations for bleeding may[6] or may not[12] be reduced. Low-dose systemic heparinization has been considered safe,[1,4–7,10,12,17,19] although one group was concerned because of a slight increase in the incidence of stroke postoperatively (2 of 15 versus 0 of 15).[3]

Our results demonstrated no significant clinical benefits of low-dose heparin administration. Hemoglobin levels remained proportionally constant throughout the observation period. Chest tube drainage did not differ among groups with the exception of a significantly lower level for group 1 at postoperative hour 20, which can be attributed to statistical artifact. Postoperative platelet counts, coagulation assays, acetylsalicylic acid administration, transfusion requirements, coagulopathies and reoperations for bleeding did not differ significantly. In the last patient to complete the study, the surgeon thought he noticed a clot in the operative field and subsequently administered additional heparin. The practice of low-dose heparinization in conjunction with the use of heparin-coated circuits appears safe, but caution is still warranted.

Centrifugal versus roller pumps

Traditionally, a roller pump system has been used to circulate blood through the CPB circuit. This has been considered traumatic to blood components, resulting in hemolysis and reduction of postoperative hemoglobin concentration, platelet consumption and the associated coagulopathy, and aggravation of the post-perfusion syndrome. A centrifugal pump might reduce blood-cell trauma and the related consequences.

Previous trials comparing roller to centrifugal pumps have demonstrated varying effects of centrifugal pumping. No benefits have been seen in terms of chest tube drainage,[25,26] transfusion requirements,[25–27] bleeding, hemoglobin[26] or hematocrit levels.[28] Studies have shown benefits in terms of platelet

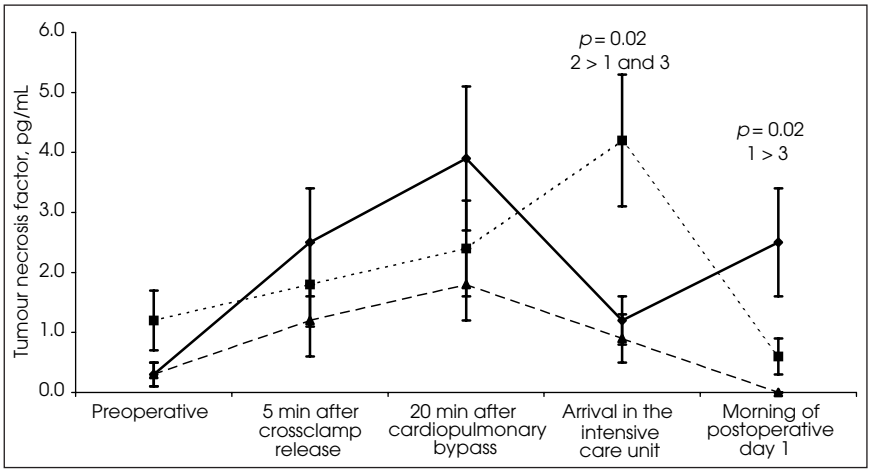

FIG. 3. Tumour necrosis factor in patients undergoing coronary artery bypass grafting using regular uncoated bypass equipment with roller pump and full-dose heparinization (group 1, diamonds), a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization (group 2, squares) or fully heparin-coated bypass equipment with a centrifugal pump and low-dose heparinization (group 3, triangles).

Table 3

Medications Used at the Three Time Measurements in the Patients Who Underwent Coronary Artery Bypass Grafting in the Three Groups

	Group				
Medication	1 (*n* = 30)	2 (*n* = 30)	3 (*n* = 26)	Overall (*n* = 86)	*p* value
Vasodilators					
Preoperative	27 (90)	20 (67)	20 (77)	67 (78)	0.09
Intraoperative	23 (77)	22 (73)	18 (69)	63 (73)	0.82
Postoperative*	24 (86)	27 (90)	21 (88)	72 (88)	0.88
ASA					
Preoperative	26 (87)	25 (83)	25 (96)	76 (88)	0.31
Postoperative*	28 (100)	30 (100)	23 (96)	81 (99)	0.30
Inotropes					
Intraoperative	14 (47)	9 (30)	12 (46)	35 (41)	0.34
Postoperative*	14 (50)	9 (30)	9 (38)	32 (39)	0.30
Tranexamic acid					
Intraoperative	27 (90)	26 (87)	20 (77)	73 (85)	0.37
Aprotinin					
Intraoperative	1 (3)	1 (3)	1 (4)	3 (3)	0.99

Variables are expressed as no. (and %).
*Group 1, *n* = 28, group 2, *n* = 30, group 3, *n* = 24, overall, *n* = 82.

Table 4

Intraoperative Variables (Mean (and SEM)) in Patients Who Underwent Coronary Bypass Grafting in the Three Groups

	Group				
Variable	1 (*n* = 30)	2 (*n* = 30)	3 (*n* = 26)	Overall (*n* = 86)	*p* value
No. of grafts	3 (1)	3 (1)	3 (1)	3 (1)	0.75
Carotid endarterectomy*	3 (10)	1 (3)	0	4 (5)	0.19
Cross-clamp time, min	63 (4)	63 (4)	60 (4)	62 (2)	0.79
Cardiopulmonary bypass time, min	97 (4)	98 (4)	95 (3)	97 (2)	0.86
Operative time, min	215 (5)	221 (7)	220 (6)	219 (3)	0.84

*Expressed as no. (and %).

counts[27,29] and function,[27] hemolysis,[27,29,30] fibrinolysis and coagulation,[28] inflammatory mediator release,[27] and blood-cell trauma as measured by β-thromboglobulin levels. Other trials have contradicted these results, demonstrating no improvements in terms of platelet count,[30–32] platelet function,[25,31] hemolysis[25,32] and inflammatory response.[26,33] In a study by Ashraf and associates,[24] centrifugal pumps were shown to elicit a greater inflammatory response than roller pumps.

Our study revealed no advantages of the centrifugal pump. Hemoglobin and platelet levels after CPB were similar among the 3 groups. Similarly, there were no changes in transfusion requirements or blood loss. Indicators of inflammatory response did not point to a more biocompatible system. These results should be interpreted with caution, however, owing to the small size of our study.

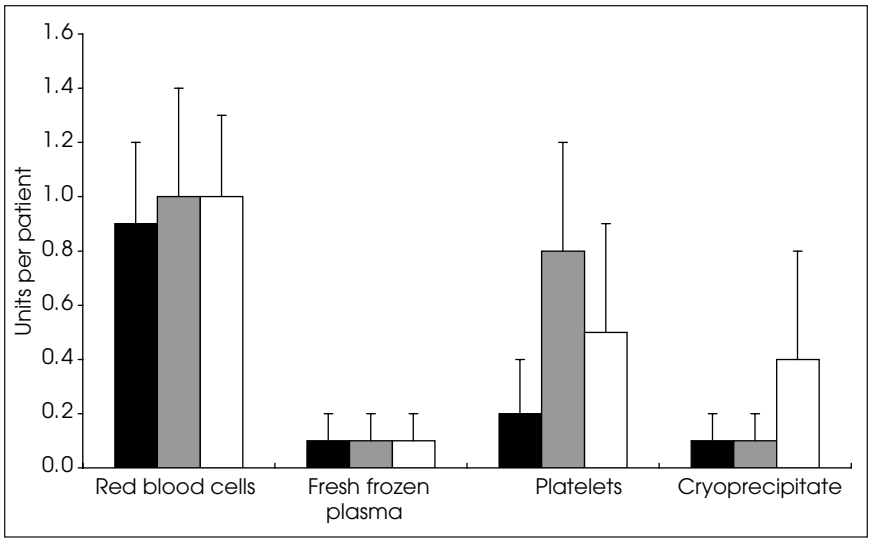

FIG. 4. Transfusion requirements in patients undergoing coronary artery bypass grafting using regular uncoated bypass equipment with roller pump and full-dose heparinization (group 1, black columns), a heparin-coated oxygenator with a centrifugal pump and full-dose heparinization (group 2, hatched columns) or fully heparin-coated bypass equipment with a centrifugal pump and low-dose heparinization (group 3, white columns).

Table 5

Postoperative Variables and Outcomes (Expressed as Mean (and SEM)) for Patients Who Underwent Coronary Bypass Grafting in the Three Groups

	Group				
Variable/outcome	1 (*n* = 28)	2 (*n* = 30)	3 (*n* = 25)	Overall (*n* = 83)	*p* value
Transfusion(s) required*	11 (39)	10 (33)	11 (48)	32 (40)	0.56
Temporary pacing*	10 (33)	8 (27)	5 (20)	23 (26)	0.52
24-h fluid balance, mL	–868 (263)	–975 (196)	–633 (232)	–836 (133)	0.58
Weight change, kg					
Day 1	0.5 (0.5)	–0.1 (0.3)	0.2 (0.5)	0.2 (0.2)	0.51
Day 2	0.6 (0.4)	–0.2 (0.4)	–0.3 (0.5)	0.03 (0.2)	0.38
Respiratory failure*	0	0	1 (4)	1 (1)	0.31
Coagulopathy*	0	0	1 (4)	1 (1)	0.31
Reoperation for bleeding*	2 (7)	0	1 (4)	3 (3)	0.37
Death*	0	0	1 (4)	1 (1)	0.31
Intubation time, h	11.5 (1.7)	14.1 (2.0)	13.9 (1.8)	13.1 (1.1)	0.38
Intensive care stay, h	28.5 (3.8)	32.1 (4.2)	31.0 (3.4)	30.5 (2.2)	0.06
Hospital stay, d	5 (1)	7 (1)	7 (1)	6 (1)	0.20

*Expressed as no. (and %).

Conclusions

We have demonstrated that CPB with a heparin-coated circuit, a centrifugal pump and low-dose systemic heparinization is comparable with respect to safety to the current practice of CPB with an uncoated circuit, a roller pump and high-dose systemic heparinization. Although heparin-coated circuits are safe, they did not confer any additional benefits over standard CPB management.

Acknowledgements: Supported by a grant from Medtronic of Canada Ltd. We would like to thank the intensive care unit nurses, anesthesiologists and perfusionists at the University of Alberta Hospital for their assistance with this study.

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Appendix 1

Transfusion Protocol

Red cells were transfused if the patient's hemoglobin level fell below 80 g/L or the hematocrit fell below 24%. In ill patients requiring a greater oxygen-carrying capacity, red cells were transfused when the hemoglobin level fell below 95 g/L or the hematocrit fell below 28%. Two units of fresh frozen plasma were administered if bleeding continued at a rate of ≥ 6 mL/kg for the first hour or ≥ 9 mL/kg for the first 3 hours, and with an international normalized ratio of ≥ 2.0. Platelets were administered if bleeding continued at the rate mentioned, and if the platelet count was ≤ 80×10^9/L. Six units of platelets were given if the count was between 50×10^9/L and 80×10^9/L. If the count fell below 50×10^9/L, 8 units were given. Eight units of cryoprecipitate were given if the fibrinogen level was ≤ 1.0 g/L with bleeding at the levels mentioned above.

Appendix 2

Criteria for Extubation

Appearance: no apprehension or diaphoresis, alert, oriented, cooperative, and responsive to verbal commands
Muscle strength: sustained head lift for 5 s
Hemodynamics: systolic arterial pressure > 90% of preoperative level, left atrial and pulmonary capillary wedge pressure < 120% of preoperative level
Temperature ≥ 36°C
Absence of bleeding: hourly chest drainage < 1 mL/kg
Fractional intake of oxygen ≤ 0.4 with Pa_{O_2} > 90 mm Hg
P_{CO_2} ≤ 42 mm Hg
Positive end-expiratory pressure ≤ 5 cm H_2O
No untreated arrhythmias