Influence of PMEA-Coated Bypass Circuits on Perioperative Inflammatory Response

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Background. **Poly(2-methoxyethylacrylate) (PMEA) is a new coating material, and several experimental studies have revealed excellent biocompatibility of PMEA-coated cardiopulmonary bypass circuits. The clinical utility of the PMEA-coated circuits was compared with that of uncoated circuits, focusing on perioperative inflammatory response.**

Methods. **Twenty-two patients were randomized to PMEA-coated (group P; Capiox RX25; n = 11) or uncoated (group U; Capiox SX10; n = 11) circuit group, and underwent coronary artery bypass grafting and/or valve operations. The following markers, as well as clinical outcomes, were analyzed perioperatively: (a) complement activation by C3a (including C3a-desArg) concentrations; (b) leukocyte activation by polymorphonuclear-elastase concentrations; (c) acute phase inflammatory response by interleukin-6 concentrations; and (d) platelet preservation by number of platelets.**

Results. **The maximal values of C3a and polymorphonuclear-elastase were significantly lower in group P than in group U. The intergroup difference of interleukin-6 was not significant. Although preservation of platelets was significantly better in group P until 1 hour after initiating cardiopulmonary bypass, no significant intergroup difference was observed thereafter. The duration of postoperative mechanical ventilation revealed no significant intergroup difference.**

Conclusions. **The PMEA-coated circuits exhibited better suppression of perioperative complement and leukocyte activation than the uncoated circuits. In addition, the price of the PMEA-coated circuits is the same as that of the uncoated circuits. Therefore, we judged that the clinical utility of the PMEA-coated circuits is superior to those of the uncoated circuits.**

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Activation of systemic inflammation is a well-known adverse effect of cardiopulmonary bypass (CPB) [1–4]. Because the contact of blood components with CPB circuits is one of the major causes of inflammation, developing hemocompatible surface coating can reduce the inflammatory response and improve the outcome of cardiac surgery. Poly(2-methoxyethylacrylate) (PMEA) is one of the new coating materials, and PMEA-coated circuits have already been reported to reduce protein and platelet adsorption and to suppress the inflammatory response in several in vitro [5–7] and animal studies [8, 9]. Although this type of circuit is now being used widely, no clinical outcomes have yet been reported. We therefore conducted a prospective and randomized clinical study on the biocompatibility of the PMEA-coated circuits, focusing mainly on the perioperative systemic inflammatory response, platelet consumption, and respiratory dysfunction.

Patients and Methods

Patients

This study was approved by the local ethical committee. Twenty-two adult patients admitted for first-time elective coronary artery bypass grafting and/or valve operations scheduled between November 1, 2000 and January 31, 2001 were included in this study after giving informed consent. Inclusion criteria were absence of major noncardiac illness, normal liver function, and no history of recent use of steroids, acetylsalicylic acid, or antiinflammatory drugs. The patients were randomly divided into two groups: group P (n = 11) and group U (n = 11). PMEA-coated circuits and oxygenators (Capiox RX25, Terumo Corp, Tokyo, Japan) were used during CPB in group P, and uncoated circuits (Capiox SX10, Terumo Corp) in group U. The randomization was conducted using a coin toss method by one of us (M.N.), and the other medical staff members were not informed of the randomization throughout the study.

Perioperative Management

Anesthesia was started and maintained with midazolam, fentanyl citrate, and vecuronium bromide. After induction of anesthesia, 300,000 U Ulinastatin and 1 g methylprednisolone were administered in all cases. The CPB circuits were primed with Ringer's lactate solution (0.5 L), 20% D-mannitol (0.2 L), 25% human serum albumin (0.1 L), 7% sodium bicarbonate (20 mL), and heparin (36 mg). After median sternotomy and systemic heparinization (3 mg/kg), CPB was instituted between the ascending aorta and both vena cavae using arterial (DLP, Medtronic, Minneapolis, MN) and venous cannulas (Sarns, Terumo Cardiovascular Systems, Ann Arbor, MI) with a nonpulsatile flow of 2.4 $L \cdot min^{-1} \cdot m^{-2}$. During CPB, activated

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clotting time was maintained at longer than 400 seconds with the additional use of heparin, and Ringer's lactate solution was added to maintain stable volume status if necessary. Blood transfusion (including an autologous supply) and extracorporeal ultrafiltration method (ECUM) (MERA Hemoconcentrator HC-100 M, Senko Medical Instrument, Tokyo, Japan) were used only after the first 2 hours of CPB if necessary, considering the timing of blood sampling described later. The ascending aorta was cross-clamped under moderate hypothermia (28° to 30°C) and cardioplegic arrest was obtained using coldblood cardioplegia (Miotector, Mochida Pharmaceutical, Tokyo, Japan). After completion of the main surgical procedures, CPB was weaned off, protamine (4.5 mg/kg) was administered, and inotropic drugs were given. Additional protamine was given, if necessary, to reestablish pre-bypass activated clotting time levels. Patients were transferred to the coronary care unit (CCU) after the operation, and received continuous positive pressure ventilation. An air-to-oxygen mixture ratio of at least 0.4 and a positive end-expiratory pressure of at least 3 mm Hg were used. These conditions were strengthened, if necessary, to keep the arterial oxygen pressure more than 100 mm Hg. Blood transfusion was used when the hematocrit (Hct) level fell below 22%. Endotracheal tubes were removed when the patients regained stable hemodynamics under low doses of inotropic drugs, normal consciousness level, and acceptable respiratory function (normocapnia and arterial oxygen pressure above 100 mm Hg with inhalation oxygen below 50%). Patients were transferred to the general ward when they were extubated and no longer required inotropic support. Clinical records were kept on major postoperative complications, the timing of extubation, and the duration of CCU stay.

Blood Sample and Analysis

Blood samples were taken at 5 time points (T1 through T5), ie, immediately before CPB, 1 and 2 hours after start of CPB, and 1 and 24 hours after the start of protamine infusion. Each blood sample was divided into two tubes containing either ethylenediaminetetraacetic acid or heparin (5 mg for 10 mL of whole blood). The tube with ethylenediaminetetraacetic acid was used immediately to obtain a complete blood count. The heparin-containing tube was immediately centrifuged at 3,500 rpm for 15 minutes, and plasma was stored at −80°C. Concentrations of complement C3a including C3a-desArg, interleukin-6 (IL-6), and polymorphonuclear-elastase (PMN-E) were then measured using the respective assay kits (Human Complement C3a des Arg assay kit, Sanwa Kagaku, Nagoya, Japan; Human IL-6 ELISA kit, Genzyme Japan, Tokyo, Japan; Polymorphonuclear Elastase EIA kit, Sanwa Kagaku).

Statistical Analysis

Statistical analysis was conducted using SPSS 10.0J for Windows (SPSS Japan, Tokyo, Japan). Continuous variables were expressed as mean ± SD. Considering the large hemodilution during CPB, data during CPB (at T2 and T3) were corrected using the Hct levels as follows: *(corrected data at T2 or T3) = (original data at T2 or T3) × (Hct at T1)/(Hct at T2 or T3)*. Because the values of platelet count had large interpatient variations, the data were expressed as the percentages against the values from before bypass so as to diminish the influence of the pre-bypass variation [10]. Two-way repeated-measures analysis of variance (ANOVA) was conducted to compare the time-dependent changes between the groups. If ANOVA revealed significant interaction terms, point-to-point comparisons between the groups were conducted using the unpaired t test. Other data obtained at one time point, such as extubation time, were compared between the groups using the unpaired t test (for continuous variables) or the χ^2 test (for categorical data). Values of p less than 0.05 were considered statistically significant.

Results

Patient characteristics and surgical data are presented in Table 1. Although the operative procedures were not completely the same between the groups, no significant differences were observed in age, sex, body weight, body surface area, operation time, CPB time, cross-clamp time, the amount of bleeding or blood transfusion, the incidence of blood transfusion, rectal temperature, the dosage of heparin or protamine, the reduced water volume with ECUM, or the incidence of ECUM.

C3a and C3a-desArg

The values of C3a including C3a-desArg are presented in Figure 1. C3a and C3a-desArg levels increased and reached a peak 1 hour after CPB initiation, gradually decreased thereafter, and nearly returned to the pre-bypass level 24 hours after CPB termination in both groups. The time-dependent curve lower in group P than in group U, and repeated-measures ANOVA revealed a significant interaction term (for interaction term $p < 0.0001$; for within-subject [time] effect $p < 0.0001$; for between-subject [group] effect $p = 0.0001$). Further comparisons revealed that the C3a and C3a-desArg levels were significantly lower in group P than in group U at 1 and 2 hours after start of CPB, and at 1 and 24 hours after CPB termination.

Polymorphonuclear-Elastase

The values of PMN-E are presented in Figure 2. PMN-E began to increase after CPB initiation and reached a peak 1 hour after CPB termination in both groups. Repeated-measures ANOVA, however, revealed a significant interaction term ($p = 0.03$; for within-subject effect $p < 0.0001$; for between-subject effect $p = 0.09$), and further comparisons revealed that the suppression of PMN-E at 1 hour after CPB termination was significantly better in group P than in group U.

Interleukin-6

The values of IL-6 are presented in Figure 3. The time-dependent changes seemed similar to those in the PMN-E study described above in both groups. Interleu-

Table 1. Patient Characteristics and Surgical Data

	Group P (PMEA-coated)	Group U (Uncoated)	p^a
Patients (n)	11	11	
Age (y)	62.6 ± 10.0	61.8 ± 13.1	0.87
Male/Female (n)	6/5	7/4	0.66
Body weight (kg)	56.2 ± 11.0	50.7 ± 7.2	0.18
Body surface area (m^2)	1.57 ± 0.17	1.50 ± 0.12	0.27
Operation (n)	CABG: 4	CABG: 2	
	Valve operation: 6	Valve operation: 9	
	CABG and valve operation: 1		
Operation time (min)	358 ± 78	365 ± 117	0.87
Cardiopulmonary bypass time (min)	177 ± 42	168 ± 61	0.69
Cross-clamp time (min)	105 ± 29	96 ± 29	0.48
Intraoperative bleeding (mL)	343 ± 339	410 ± 317	0.64
Intraoperative blood transfusion (mL)	556 ± 634	767 ± 870	0.54
Incidence of intraoperative blood transfusion, n/N (%)	9/11 (82)	10/11 (91)	0.53
Rectal temperature (°C)	27.8 ± 1.5	28.2 ± 2.7	0.69
Dosage of heparin (mg)	173 ± 37	156 ± 20	0.19
Dosage of protamine (mg)	281 ± 68	274 ± 40	0.78
Reduced water volume with ECUM (mL)	555 ± 701	592 ± 575	0.89
Incidence of ECUM, n/N (%)	6/11 (55)	5/11 (45)	0.67
Bleeding during the first 24 h postoperatively (mL)	634 ± 349	566 ± 299	0.63
Blood transfusion during the first 24 h postoperatively (mL)	404 ± 438	462 ± 895	0.85

[a] None of the differences between the groups were significant.

Values are mean ± SD unless otherwise noted.

CABG = coronary artery bypass grafting; ECUM = extracorporeal ultrafiltration method; PMEA = poly(2-methoxyethylacrylate).

kin-6 concentrations gradually increased after CPB initiation, reached a peak 1 hour after CPB termination, and remained at high levels even 24 hours after CPB termination. Repeated-measures ANOVA revealed that the interaction term was not significant ($p = 0.84$; for within-subject effect $p < 0.0001$; for between-subject effect $p = 0.67$).

Platelets

The platelet count ratios to the pre-bypass level are presented in Figure 4. In group U, platelets began to decrease 1 hour after CPB initiation, reached a nadir 2 hours after CPB initiation, and then gradually recovered after CPB termination. In group P, platelets did not decrease until 1 hour after CPB initiation, and acutely

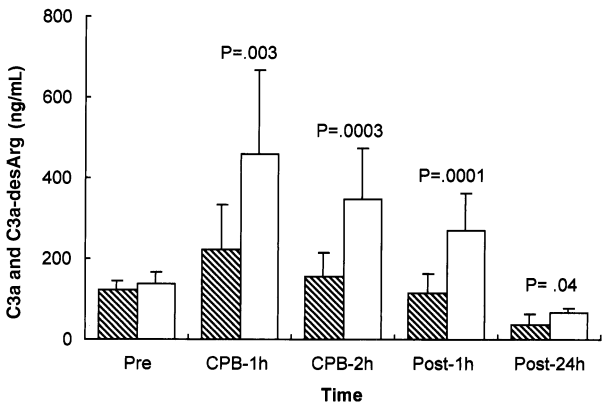

Fig 1. Complement C3a including C3a-desArg reached a peak 1 hour after cardiopulmonary bypass (CPB) initiation, and then gradually decreased in both groups. During and after CPB, the C3a and C3a-desArg levels were significantly lower in the group that received PMEA-coated circuits (group P) than in the uncoated circuit group (group U). ▨ = group P; □ = group U.

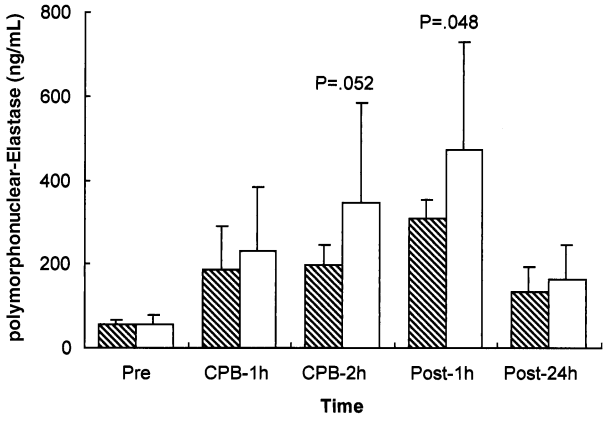

Fig 2. Polymorphonuclear-elastase increased after cardiopulmonary bypass (CPB) initiation and reached a peak 1 hour after CPB termination (Post-1h) in both groups. The peak value was significantly lower in the group that received PMEA-coated circuits (group P) than in the uncoated circuit group (group U). ▨ = group P; □ = group U.

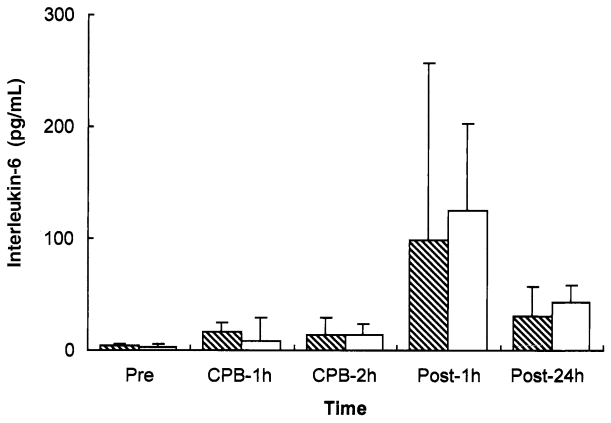

*Fig 3. Interleukin-6 gradually increased after cardiopulmonary bypass (*CPB*) initiation and reached a peak 1 hour after CPB termination (*Post-1h*) in both the group that received PMEA-coated circuits (group P) and in the uncoated circuit group (group U). The intergroup difference was not statistically significant. ▨ = group P; □ = group U.*

decreased to nearly the same level as in group U 2 hours after CPB initiation. Repeated-measures ANOVA revealed a significant interaction term ($p = 0.004$; for within-subject effect $p < 0.0001$; for between-subject effect $p = 0.08$), and preservation of platelets at 1 hour after CPB initiation was significantly better in group P than in group U.

Clinical Outcomes

After the operation, no patient died, and no major complications were observed except for prolonged tracheal intubation in some patients as described below. The duration of the postoperative mechanical ventilation was 13.3 ± 4.5 hours in group P and 26.3 ± 23.0 hours in group U, and the intergroup difference could have been due to chance ($p = 0.080$). The duration of CCU stay was 2.8 ± 2.4 days in group P and 3.2 ± 1.9 days in group U, and the intergroup difference could have been due to chance ($p = 0.70$).

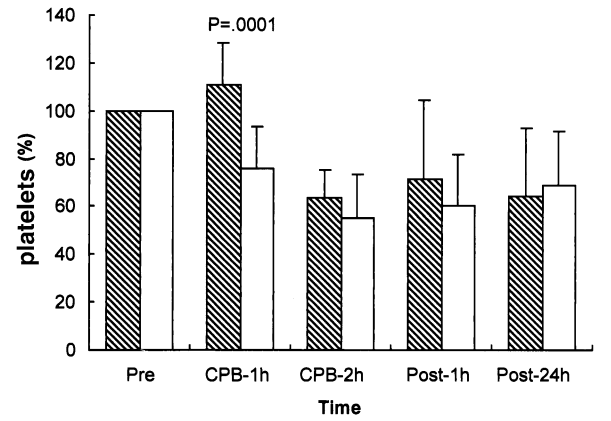

*Fig 4. Platelets began to decrease immediately after cardiopulmonary bypass (*CPB*) initiation and reached a bottom 2 hours after CPB initiation in the uncoated circuit group (group U). However, platelets were not decreased until 1 hour after CPB initiation in the group that received PMEA-coated circuits (group P). The preservation of platelets at 1 hour after start of CPB was significantly better in group P. ▨ = group P; □ = group U.*

Comment

PMEA is a polymer of acrylates, which are widely used for biomedical applications, and the outer side of the PMEA molecule is chemically inactive [5]. PMEA coating is therefore expected to improve hemocompatibility of CPB circuits, and in fact, several experimental studies have supported the advantages of PMEA-coated CPB circuits. Onishi and colleagues [6] conducted in vivo studies and reported that PMEA had excellent hemocompatibility in terms of platelet adhesion, leukocyte activation, complement activation, and coagulation. Tanaka and associates [7] reported that proteins adsorbed on the PMEA-coated surface suffered little conformational change and speculated that this feature led to reduced platelet adhesion. Saito and colleagues [8] used PMEA-coated circuits in a swine CPB model, and reported PMEA-coated circuits suppressed the adsorption of proteins including immunoglobulin G and immunoglobulin M, which would activate C3 through the classic pathway. Suhara and coworkers [9] also used PMEA-coated circuits in a swine CPB model, and reported superior preservation of platelets, reduced plasma levels of thrombin–antithrombin complex and bradykinin, and reduced amount of adsorbed fibrinogen. In addition, PMEA coating does not have adverse effects on the gas-transfer performance of oxygenators. Under the same conditions (bovine blood flow = 4 L/min, gas flow = 4 L/min), O_2 transfer was 221.2 ± 10.7 mL/min for the PMEA-coated oxygenator and 216.5 ± 6.6 mL/min for the uncoated oxygenator, and CO_2 transfer was 197.5 ± 5.2 and 195.0 ± 4.0 mL/min, respectively (data were obtained from Terumo Corp). Considering all this experimental evidence, PMEA-coated circuits are expected to exhibit good biocompatibility in clinical use as well.

In this study, we tested the clinical utility of the PMEA-coated CPB circuits using the commercially available PMEA-coated circuit set including the PMEA-coated oxygenator. We compared the PMEA-coated circuits with uncoated circuits, which had been used for a long time at our institution, in terms of complement activation (C3a including C3a-desArg), leukocyte activation (PMN-E), acute phase inflammatory cytokine induction (IL-6), platelet consumption, and organ, especially respiratory, dysfunction.

The C3a and C3a-desArg levels were clearly lower in group P than in group U during and after CPB in this study. We think this finding is important because C3a is induced mainly by the contact of blood with CPB circuits during CPB and leads to clinically undesirable responses such as the induction of inflammatory cytokines or the activation of leukocytes, which would eventually cause systemic inflammation and organ dysfunction [2–4].

PMN-E and IL-6 reached a peak a little later than C3a, at 1 hour after CPB termination. Although the intergroup difference of IL-6 was not significant, the peak value of PMN-E was significantly lower in group P. We believe that the suppressed complement activation in group P contributed to the lower peak PMN-E value. Although the influence of blood transfusion on the values of PMN-E or IL-6 was not eliminated completely, we thought the intergroup comparison was justified because the intergroup difference in the amount or incidence of blood transfusion was not significant.

As for the clinical outcomes, the intergroup difference of the duration of mechanical ventilation was not significant. We speculated that this finding was partly due to the relatively small sample size of this study.

Platelets were well preserved until 1 hour after CPB initiation in group P and acutely decreased to nearly the same level as in group U thereafter. This finding was somewhat different from that of Suhara and colleagues [9], ie, complete preservation of pre-bypass level of platelets until at least 2 hours after CPB initiation with the PMEA-coated circuits in a swine model. In actual operations, many factors such as blood loss and implantation of a prosthetic valve affect platelet consumption and may cause such a difference between clinical and experimental findings.

Heparin-coated CPB circuits, which have been reported to be superior to uncoated circuits in terms of postoperative systemic inflammation in numerous publications [10–12], were not tested in this study. Although comparing the advantages and disadvantages of the PMEA-coated circuits with the heparin-coated circuits requires more data, the relatively low price of the PMEA-coated circuits is worth mentioning. The price of the PMEA-coated circuits is the same as that of the uncoated circuits and is 33% lower than that of the heparin-coated circuits supplied by the same company (Terumo Corp). In addition, the PMEA-coated circuits are thought to be better for patients with heparin allergy.

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INVITED COMMENTARY

The clinical study of Ninomiya and colleagues is an encouraging addition to biomaterial research in cardiopulmonary bypass. The findings related to complement activation from this report are affirmative as they are consistent with the findings and predictions of in vitro studies with this surface, and they have been reproducible in several clinical trials. Inhibition of complement activation is also the most reproducible surrogate marker of the efficacy of heparin-coated surfaces; however, the molecular interactions by which the latter achieves this are not as well categorized as poly(2-methoxyethylacrylate) (PMEA).

Poly(2-methoxyethylacrylate) represents one of a novel group of coatings engineered to positively enhance protein adsorption from blood, such that the proteins appear to coat the surface in an unaltered form. For example, when fibrinogen undergoes a conformational change after adsorption to other biomaterials, it is more likely to result in platelet adhesion and activation than if its structure is identical to that the cells "see" in circulating blood. The weight of evidence from this and other research is directing us to abandon the concept of trying to design biomaterial surfaces that completely inhibit protein adsorption. These attempts have inexorably failed and often they result in unpredictable blood activation in vivo. Protein adsorption is inevitable; we have to design surfaces to preferentially adsorb the right proteins in the right configuration.

To complete the picture, future in vitro and in vivo studies with PMEA need to address whether this surface is also relatively thromboresistant, and if so, to characterize the mechanism. Regardless, it would appear that PMEA has intrinsic antiinflammatory properties, but it remains to be seen whether these biochemical changes are associated with improved clinical outcomes. How-

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