

Inflammatory Response after Coronary Revascularization: Off-pump versus On-pump (Heparin-coated Circuits and Poly2methoxyethylacrylate-coated Circuits)

Shiro Hazama, MD, Kiyoyuki Eishi, PhD, Shiro Yamachika, MD, Manabu Noguchi, MD, Tsuneo Ariyoshi, MD, Hideaki Takai, MD, Tomohiro Odate, MD, Seiji Matsukuma, MD, Daisuke Onohara, MD, and Makoto Yanatori, MD

Objective: Off-pump coronary artery bypass grafting (OPCAB) may reduce the inflammatory response associated with cardiopulmonary bypass (CPB) and contribute to minimizing postoperative complications. Heparin-coated circuits and poly2methoxyethylacrylate (PMEA)-coated circuits were developed to reduce such complications. We compared the postoperative inflammatory response with or without CPB.

Methods: Eighteen consecutive patients undergoing isolated coronary artery bypass grafting (CABG) were divided into three groups: OPCAB group (n=6), heparin-coated circuits group (n=6), PMEA-coated circuits group (n=6). The plasma concentrations of the following inflammatory markers were measured: cytokines {interleukin (IL-10)}, polymorphonuclear elastase (PMNE), coagulofibrinolytic factor {thrombin-antithrombin III complex (TAT)}, complement factor (C3a).

Results: At the end of CPB, IL-10 and TAT concentrations were significantly different among the three groups (OPCAB group < PMEA-coated group < heparin-coated group). The PMNE concentration was significantly lower in the OPCAB group and the heparin-coated group as compared to the PMEA-coated group both at the end of CPB and 4 hours after CPB. C3a concentration was significantly lower in the OPCAB group than in the CPB groups at the end of CPB. Clinical variables did not differ significantly among the three groups.

Conclusion: Off-pump CABG is associated with a reduction in the inflammatory response when compared with on-pump CABG, using either PMEA-coated or heparin-coated circuits. (*Ann Thorac Cardiovasc Surg* 2004; 10: 90–6)

Key words: off-pump coronary artery bypass grafting (OPCAB), poly2methoxyethylacrylate (PMEA), cardiopulmonary bypass (CPB)

Introduction

Cardiopulmonary bypass (CPB) has been shown to stimulate the inflammatory response and increase postoperative morbidity.¹⁻¹⁰ Recent studies in patients undergoing

From Department of Cardiovascular Surgery, Nagasaki University School of Medicine, Nagasaki, Japan

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Address reprint requests to Shiro Hazama, MD: Department of Cardiovascular Surgery, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.

a bypass graft operation have reported that off-pump coronary artery bypass grafting (OPCAB) reduces the inflammatory response and avoids postoperative morbidity.¹¹⁻¹⁵ On the other hand, it has also been reported that heparin-coated circuits reduce the inflammatory response associated with CPB.¹⁶⁻²⁰ As well, new polymer-coated (Xcoating™) circuits, in which the blood-contacting surface is coated with poly2methoxyethylacrylate (PMEA), have been developed, and they appear to have increased biocompatibility.²¹⁻²³ Therefore, to evaluate these three approaches, we compared the postoperative inflammatory response and the clinical outcome of three groups

Table 1. Clinical data

Variables	X coating	Heparin coating	OPCAB	P-value
No. of patients	6	6	6	
Male/female	4/2	2/4	4/2	
Age (y)	70.0±5.0	68.7±7.9	77.8±5.1	P<0.05
BSA (m ²)	1.52±0.14	1.45±0.13	1.59±0.17	NS
LVEF (%)	51.0±15.6	70.8±12.4	64.2±15.7	NS
No. of grafts	3.2±0.7	2.8±0.8	2.3±0.5	NS
Operating time (min)	293±46	297±66	281±32	NS
ECC time (min)	119±33	121±27		NS
AoX time (min)	78±28	76±23		NS

BSA, body surface area; LVEF, left ventricular ejection fraction ; ECC time, extracorporeal circulation time; AoX time, aortic cross-clamp time.

(OPCAB, heparin-coated, PMEA-coated) of patients undergoing coronary artery bypass grafting (CABG).

Patients and Methods

Between March 2000 to January 2003, 18 patients undergoing their first CABG were studied. They were divided into three groups; the OPCAB group, the heparin-coated group, and the PMEA-coated group. In the heparin-coated group, CAPIOX-SX(HP) (Termo Corporation, Tokyo, Japan) was used. In the PMEA-coated group, CAPIOX-RX (Termo Corporation) was used. Exclusion criteria included malignancy, autoimmune disease, and coagulopathy. Informed consent was obtained from all patients prior to the operation.

The anesthetic technique was standardized for all patients. After premedication, general anesthesia was induced and maintained with a high dose of fentanyl (0.1 mg/kg), nitrous oxide, and vecuronium bromide. In all groups a full median sternotomy was done, and internal mammary artery and/or radial artery and/or saphenous vein grafts were harvested. In the OPCAB group, we used a local cardiac wall restraining device (OctopusIII, Medtronic, Inc., Minneapolis, MN, USA), on the beating heart. A shunt tube (AXIUS™ shunt, GUIDANT, Tokyo, Japan) was used to maintain distal perfusion. The coronary artery was not clamped. Before anastomosis, heparin (100 IU/kg) was infused intravenously. In both CPB groups, the extracorporeal circuit and the oxygenator were primed with 1.8 L of 20% D-mannitol (5 mL/kg), 6% hydroxyethyl starch (5 mL/kg), and Ringer’s lactate solution without blood. Nonpulsatile extracorporeal circulation was initiated at a perfusion index of 2.4 L/min/m² body surface area using a roller pump. After administration of an initial prebypass bolus dose of heparin (150 IU/kg), whole blood activated clotting time was main-

tained at greater than 300 seconds for the entire duration of CPB with intermittent intravenous heparin administration. Moderate hypothermia, with the rectal temperature between 28°C and 32°C, was maintained. Myocardial protection was provided by injecting a cold cardioplegic solution (4°C). After CPB, protamine sulfate (150 IU/kg) was administered.

Blood samples were collected at the following times in the OPCAB group: before anastomosis and 30 min, 4 hours and 24 hours after total anastomosis. In both CPB groups blood samples were collected immediately before CPB and after CPB, and 4 and 24 hours after CPB. Plasma samples were separated immediately by centrifugation (3,000 rpm) for 15 minutes at 4°C. They were then stored at -80°C until they were analyzed with an enzyme-linked immunosorbent assay (ELISA) kit (PMN-E, E Merck, Darmstadt, Germany; TNF-α and IL-1p, BioSource Europe S.A., Nivelles, Belgium; C5b-9, Quidel, San Diego, CA). The body weight percent ratio (%R-BW) determined just after intensive care unit (ICU) admission and 24 hours after the operation was used as an indicator of the post-operative body weight gain. Hematocrit (Hct) was measured before the operation and 24 hours after the operation.

Statistical analysis

All parameters are expressed as the mean values ± the standard error. The Mann-Whitney U test and non-repeated ANOVA were used for intragroup comparisons. All computations were performed using SPSS statistical software packages (SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered significant.

Results

The clinical characteristics and operative data are shown in Table 1. The three groups were similar except that pa-

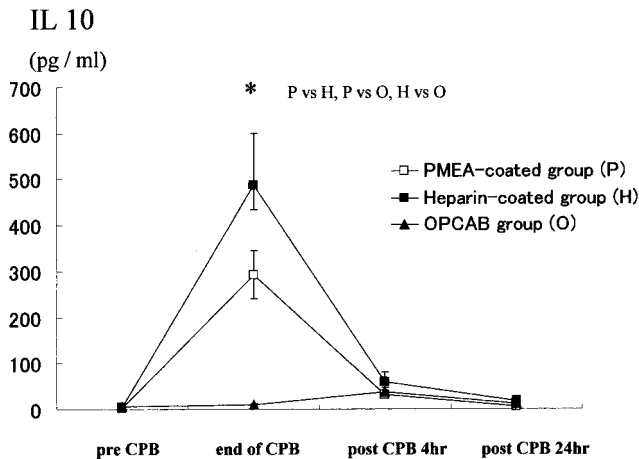


Fig. 1. Changes in IL-10 concentrations.
* P<0.05 in-between groups

tient age was significantly higher in the OPCAB group than in both CPB groups (P<0.05).

Interleukin-10

In both CPB groups, the IL-10 concentrations reached a peak at the end of CPB and decreased gradually. At the end of CPB, IL-10 concentrations in the PMEA-coated group were significantly lower than in the heparin-coated group (P<0.05). In the OPCAB group, IL-10 concentrations did not increase during the same time period. Overall, there were significant differences in IL-10 concentrations between the OPCAB group and the CPB groups (P<0.05) (Fig. 1).

Polymorphonuclear elastase (PMNE)

In the PMEA-coated group, the polymorphonuclear elastase (PMNE) concentrations reached a peak at the end of CPB, and then remained at high levels until 24 hours after CPB. In the heparin-coated group, the PMNE concentrations began to increase steadily and reached a peak 24 hours after CPB. At the end of CPB and 4 hours after CPB, PMNE concentrations in the heparin-coated group were significantly lower than in the PMEA-coated group (P<0.05). In the OPCAB group, the PMNE concentrations became gradually elevated, and reached a peak 24 hours after anastomosis. At the end of CPB and 4 hours after CPB, PMNE concentrations in the OPCAB group were significantly lower than in the PMEA-coated group (P<0.05). However, there were no significant differences in PMNE concentrations between the OPCAB group and the heparin-coated group at any time (Fig. 2).

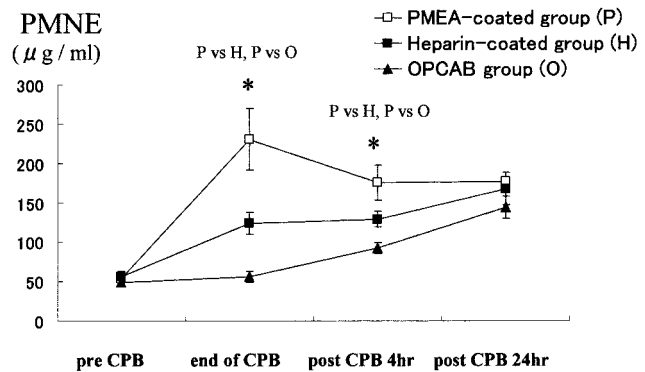


Fig. 2. Changes in PMNE concentrations.
* P<0.05 in-between groups

Thrombin-antithrombin III complex (TAT)

In both CPB groups, the TAT concentrations reached a peak at the end of CPB and then decreased gradually. In the OPCAB group, the TAT level reached a peak 4 hours after anastomosis, and decreased 24 hours after anastomosis. At the end of CPB, there were significant differences among the three groups (P<0.05) (Fig. 3).

C3a

The concentration of C3a in the CPB groups reached a peak at the end of CPB. In the OPCAB group, the concentration of C3a did not change significantly over time. The concentration of C3a was significantly lower in the OPCAB group than in both CPB groups at the end of CPB (P<0.05). There were no significant differences between the CPB groups over time (Fig. 4).

Postoperative clinical variables

The postoperative clinical data are summarized in Table 2. There were no deaths or postoperative complications in this series. There were no significant differences among the three groups in postoperative blood loss over the first 24 hours, intubation time, and ICU stay. While there were no statistically significant differences in % weight gain (%R-BW) among the three groups (Fig. 5), the %R-BW was least in the OPCAB group, and greatest in the heparin-coated group. Postoperative Hct change was significantly lower in the OPCAB group as compared to the CPB groups (P<0.05) (Fig. 6).

Comment

Over the last decade, a number of unfavorable reactions related to CPB have been reported.¹⁻⁴⁾ The post-pump in-

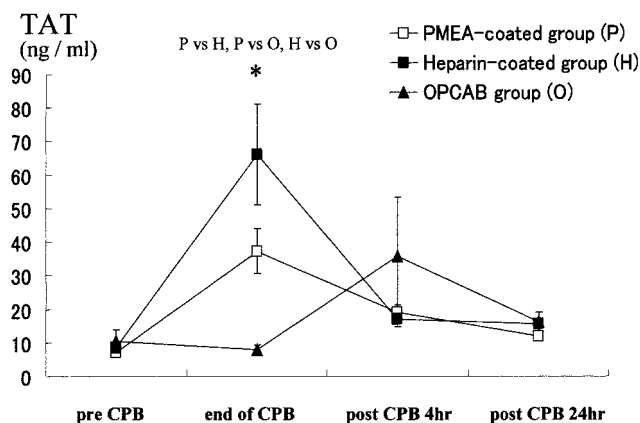


Fig. 3. Changes in TAT concentrations.

* P<0.05 in-between groups

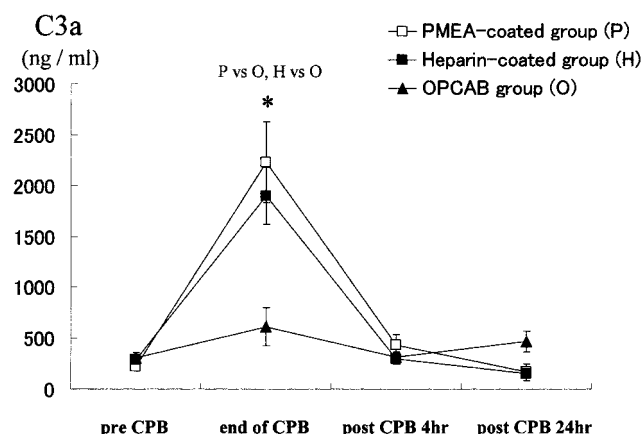


Fig. 4. Changes in C3a concentrations.

* P<0.05 in-between groups

flammatory response is believed to be caused by the blood's contact with foreign materials, and its exposure to abnormal shear forces.²⁴⁾ Consequently, the reduction of these adverse inflammatory responses is still a matter of concern.

It has been established that the systemic inflammatory response to CPB is characterized by the activation of the coagulation, fibrinolytic, kallikrein, and complement cascades, and it is associated with significant morbidity and mortality.²⁵⁾ This generalized reaction is complex and eventually leads to leukocyte stimulation and adhesion to the microvasculature. Increased adhesion of platelets to leukocytes has also been demonstrated as part of the systemic response. Such adhesion produces protein complexes whose surfaces may regulate contact activation of the complement and coagulation cascades. Neutrophil activation also results in the generation of oxygen free radicals and the release of powerful serine proteases, specifically elastase, collagenase, and gelatinase, causing significant injury to the endothelium in the capillary bed. Whether this process represents reperfusion injury or contact activation of blood components, especially complement, remains unresolved. Recent studies have suggested

that the use of heparin-coated circuits could attenuate the intensity of the inflammatory reaction with respect to cytokine release and neutrophil activation.^{16,17)} Therefore, numerous studies have been undertaken in order to demonstrate whether there are any postoperative clinical benefits due to heparin-coated CPB.^{18,19)} Terumo Corporation, however, developed polymer-coated extracorporeal circuits in which the blood-contacting surfaces are coated with PMEA, based on the hypothesis that minimizing surface protein adsorption, would decrease surface-biocomponent interactions and thereby enhance biocompatibility. The amount of protein adsorbed onto the PMEA-coated circuits is significantly lower than that adsorbed onto uncoated circuits.²¹⁻²³⁾ On the other hand, OPCAB may reduce the postoperative inflammatory response associated with CPB, since circulating blood is not in contact with artificial surfaces, and this may minimize the risk of postoperative morbidity. Bashir and colleagues reported that an off-pump CABG on a beating heart significantly reduces oxidative stress and suppresses the inflammatory reaction associated with the use of CPB.¹²⁾ They reported that complement C3a and elastase levels were rapidly increased upon the institution of CPB,

Table 2. Postoperative data

Variables	X coating	Heparin coating	OPCAB	P-value
Mortality	0	0	0	
Stroke	0	0	0	NS
Total blood loss (ml)	803±245	1,047±620	1,310±429	NS
Transfusion (unit)	3.3±2.2	2.7±2.4	2.3±3.2	NS
Intubation time (hr)	9.0±5.9	6.5±4.2	7.2±4.8	NS
ICU stay (day)	4.2±1.1	4.7±1.6	4.5±2.6	NS

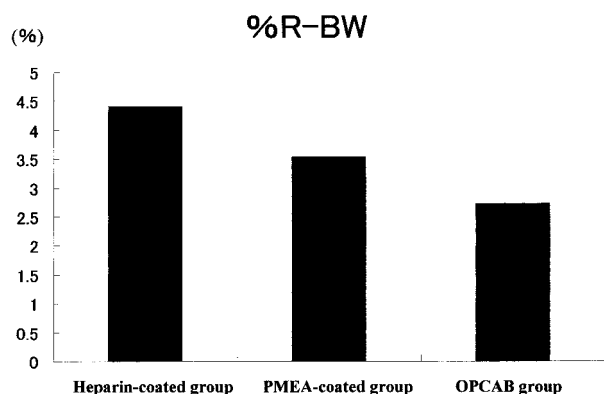


Fig. 5. %R-BW.

No significant differences between the groups

and that this was followed by increases in IL-8, TNF- α , and sE-selection. In contrast, the rise of these factors was blunted in patients undergoing operation without CPB. Ascione and colleagues also reported that CABG performed on a beating heart is associated with significant reductions in the inflammatory response and the postoperative infection rate when compared to conventional revascularization with CPB and cardioplegic arrest.¹¹⁾ It has been found that IL-10 exerts a number of anti-inflammatory effects, including inhibiting the synthesis of proinflammatory cytokines. Since increased levels of IL-10 have been found during CPB following increases of proinflammatory cytokines, this may represent an endogenous anti-inflammatory response. In our study, at the end of CPB, the concentration of IL-10 was significantly lower in the PMEA-coated group than in the heparin-coated group. These differences disappeared 4 hours and 24 hours after CPB. In the OPCAB group, the IL-10 concentrations were not significantly elevated at any time. At the end of CPB, the IL-10 level was significantly lower in the OPCAB group than in the CPB groups.

The anaphylatoxins C3a and C5a, as well as the C5b-9 terminal complex, have been shown to be elevated during CPB. Complement products have been associated with an increase in neutrophil adhesion and degranulation, and they have also been shown to increase the production of IL-1 and TNF- α , both of which are known to induce synthesis of IL-6.¹⁾ C3a levels usually peak at the end of CPB, and this is known to be related to the duration of CPB. C3a levels then return to pre-CPB values 24 to 48 hours postoperatively. Hahn-Pederson and associates suggested that the mild elevation of C3a observed in the off-pump group could be related to surgical manipulation.²⁶⁾ In our

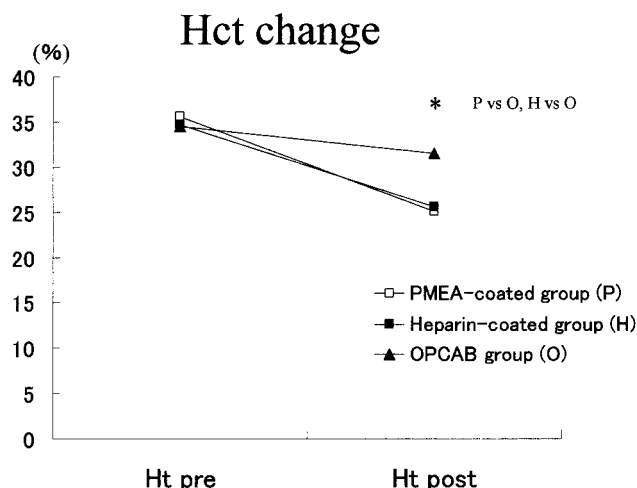


Fig. 6. Changes in Hct.

* P<0.05 in-between groups

study, C3a reached a peak at the end of CPB in both CPB groups. Furthermore, there were no significant differences between the heparin-coated group and the PMEA-coated group. In the OPCAB group, C3a was mildly elevated at the end of CPB, but it was significantly lower than in both CPB groups.

Complement activation may lead to neutrophil activation. The degree of inflammation induced by neutrophil activation is thought to be related to the serum level of neutrophil elastase, which is an endopeptidase that has been used as a marker of neutrophil activation.²⁷⁾ Neutrophil elastase was significantly lower in the heparin-coated group than in the PMEA-coated group at the end of CPB and 4 hours after CPB. However, these differences disappeared 24 hours after CPB. In the OPCAB group, the PNME level increased gradually, and reached a peak 24 hours after CPB. There were no significant differences between the OPCAB group and the heparin-coated group in the PNME levels at any time.

It has been reported that heparin-coated circuits improve thromboresistance, increase biocompatibility, and suppress the activation of complement components and granulocytes.²⁸⁾ However our data showed that TAT was significantly lower in the PMEA-coated group than in the heparin-coated group at the end of CPB. At the same time point, in the OPCAB group the TAT level was significantly lower as compared to either of the CPB groups.

In our study, postoperative clinical data failed to demonstrate any definite benefits for any of the three groups. Postoperative blood loss, blood transfusion, intubation time, and the length of ICU stay were not significantly

different among the three groups. Wagner and colleagues have reported that the use of a heparin-coated CPB circuit did not provide significant benefits with respect to postoperative blood loss or hemostatic alterations.¹⁸⁾ Our data also indicate that the heparin-coated CPB circuit did not reduce postoperative blood loss.

Although there were no significant differences in postoperative %R-BW between the three groups, it tended to be lower in the OPCAB group. As well, postoperative Hct change was significantly lower in the OPCAB group as compared with the CPB groups. This would suggest that the body fluid shift is lower in the OPCAB group.

Conclusion

This study shows that OPCAB is associated with a reduction in the inflammatory response when compared to on-pump CABG. PMEA-coated circuits and heparin-coated circuits had similar effects on the inflammatory response. Although we could not show any postoperative clinical advantages in the off-pump group, postoperative weight gain and Hct decline were lower in the off-pump group than in either CPB group. This suggests that the body fluid shift is lower in OPCAB patients.

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