J Artif Organs (2003) 6:245–252
DOI 10.1007/s10047-003-0237-5

ORIGINAL ARTICLE

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Clinical study of biocompatibility between open and closed heparin-coated cardiopulmonary bypass circuits

Abstract The objective of this study was to investigate the difference between the closed circuit system and the open circuit system in clinical heparin-coated cardiopulmonary bypass (CPB) circuits with a centrifugal pump. We evaluated the coagulation, fibrinolysis, and inflammatory response in valvular heart surgery. Nineteen patients were assigned at random to a group for the closed circuit system or the open circuit system. This is the first report on the effect of a closed circuit in valvular surgery. We measured the platelet count, white blood cell count, plasma fibrinogen concentration, thrombin–antithrombin III complex, plasmin-α2 plasmin inhibitor complex, D-dimer, interleukin-6, polymorphic neutrophil-elastase, and the plasma free hemoglobin. Blood samples were collected before the start of perfusion, 15 and 60 min after the start of perfusion, 60 min after the administration of protamine, and 1 day after the operation. During the perfusion, coagulation, fibrinolysis, and inflammatory responses were activated; however, no significant differences between the two groups were noted. In this clinical investigation with suction and the cell saving system, the closed circuit was not found to be superior to the open circuit with regard to biocompatibility.

Key words Cardiopulmonary bypass · Heparin-coated · Closed circuit · Open circuit

Received: November 12, 2002 / Accepted: September 3, 2003

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Introduction

It is reported that the heparin-coated circuit suppresses the coagulation system and inflammatory response during cardiopulmonary bypass (CPB).[1–3] In addition, the centrifugal pump was reported to be more biocompatible than the roller pump,[4] and the closed circuit was reported to be superior to the open circuit in in vitro studies and in clinical coronary artery bypass grafting (CABG).[5,6] The closed type heparin-coated circuit seems to be advantageous because contact of the blood with foreign material and air is effectively minimized. There are no reports on the biocompatibility of the closed circuit in clinical valvular surgery. Here, we compare the coagulation, fibrinolysis, and inflammatory response of heparin-coated CPB equipment between an open circuit system and a closed circuit system in clinical valvular surgery.

Patients and methods

This clinical study included nineteen patients (Table 1). The patients were assigned at random to one of two groups: the closed circuit group (group C, $n = 9$) and the open circuit group (group O, $n = 10$). The nineteen patients consisted of ten patients for aortic valve replacement, three patients for mitral valve replacement, two patients for mitral valvuloplasty, two patients for open mitral commissurotomy, and two patients for the maze operation. There were twelve men and seven women in the study group. Between the open and closed circuit groups, there was no significant difference in terms of age (C versus O; 67.0 ± 8.7 versus 58.8 ± 9.4 years), gender, pump time (188.9 ± 36.0 versus 167.7 ± 71.1 min), aortic cross clamp time (133.2 ± 21.3 versus 104.3 ± 40.1 min), and the blood transfusion ratio and amount (2/9, 2.0 ± 2.8 vs 2/10, 1.4 ± 3.3 units).

In both groups, the extracorporeal circuit consisted of a heparin-coated hollow-fiber membrane oxygenator

Table 1. Patient characteristics

	Closed circuit group	Open circuit group
Number of patients	9	10
Age (years)	67.0 ± 8.7	58.8 ± 9.4
M/F	5/4	7/3
Operation	AVR 5, MVP 2, MVR 1, MAZE 1	AVR 5, MVR 2, OMC 2, MAZE 1
Pump time (min)	188.9 ± 36.0	167.7 ± 71.1
Aortic cross clamp time (min)	133.2 ± 21.3	104.3 ± 40.1
Transfusion ratio and amount (units)	2/9 (2.0 ± 2.8)	2/10 (1.4 ± 3.3)

Values are expressed as the mean with standard deviation of the mean
No significant differences were observed between the two groups
AVR, aortic valve replacement; MVP, mitral valvuloplasty; MVR, mitral valve replacement; OMC, open mitral commissurotomy; MAZE, Maze operation

Table 2. Characteristics of the cardiopulmonary circuit

Circuit	Closed circuit group	Open circuit group
Pump tubing	Edwards Lifesciences	Edwards Lifesciences
Artificial lung	Platinum Cube NCVC6000, Dainippon Ink and Chemicals	Platinum Cube NCVC6000, Dainippon Ink and Chemicals
Centrifugal pump	HPM-15, Nikkiso	HPM-15, Nikkiso
Venous reservoir	BMR1900G (soft reservoir), Jostra Bentley	BMR4500SG (hard shell reservoir), Jostra Bentley
Cardiotomy reservoir	BCR3500G, Jostra Bentley	
Arterial filter	AF-2040G, Jostra Bentley	AF-2040G, Jostra Bentley

(Platinum Cube NCVC 6000, Dainippon Ink and Chemicals, Tokyo, Japan), centrifugal pump (HAP-15, Nikkiso, Tokyo, Japan), arterial line filter (AF-2040G, Jostra Bentley, Irvine, CA, USA) and heparin-coated tubing (Edwards Lifesciences, Irvine, CA, USA). In group C, a collapsible soft shell venous reservoir (BMR1900G, Jostra Bentley) with a cardiotomy reservoir (BCR3500G, Jostra Bentley) was used. In group O, a hard shell venous reservoir (BMR4500SG, Jostra Bentley) was used (Table 2). In all cases, a cardiotomy suction system, a left atrial and aortic venting system, and a cell saving system were used.

Following systemic heparinization (300 IU/kg), CPB was initiated when the activated clotting time (ACT) was maintained at >400 s; additional heparin (in boluses of 5000 IU) was used when necessary. After termination of CPB, heparin was neutralized with protamine at a 1:1 ratio. Blood was sampled before the start of perfusion, at 15 and 60 min after the start of perfusion, at 60 min after the administration of protamine, and 1 day after the operation. The platelet count, white blood cell (WBC) count, fibrinogen, thrombin–antithrombin complex (TAT), plasmin-α2 plasmin inhibitor complex (PIC), D-dimer (DD), interleukin-6 (IL6), polymorphic neutrophil- (PMN) elastase, and plasma free hemoglobin were measured. Statistical analysis was done with the Statview program (SAS Institute, Cary, NC, USA, version 5,0,0,0) The χ^2 test was used for the nonparametric variables and the two-way repeated measures analysis of variance (ANOVA) was used for continuous variables. A P value of less than 0.05 was regarded as statistically significant. All data are presented as mean ± standard deviation (SD) unless stated otherwise.

Results

No patients required reoperation for surgical bleeding. None of the patients died during hospitalization.

White blood cells

The number of WBCs increased 60 min after initiation of CPB (Fig.1) and remained slightly high at 1 day after the operation. No significant differences were noted between the two groups.

Platelets

The number of platelets decreased during CPB (Fig. 2) and had not returned to the preoperative level at 1 day after the surgery (C:9.1 ± 3.4 × 10^4, O:10.8 ± 2.8 × 10^4). No significant differences were noted between the two groups.

Fibrinogen

The fibrinogen level decreased during CPB and returned to the preoperative level after the operation (Fig. 3). The lowest value was measured at 15 min after perfusion started (C:153 ± 29, O:156 ± 46 mg/dl). No significant differences were noted between the two groups.

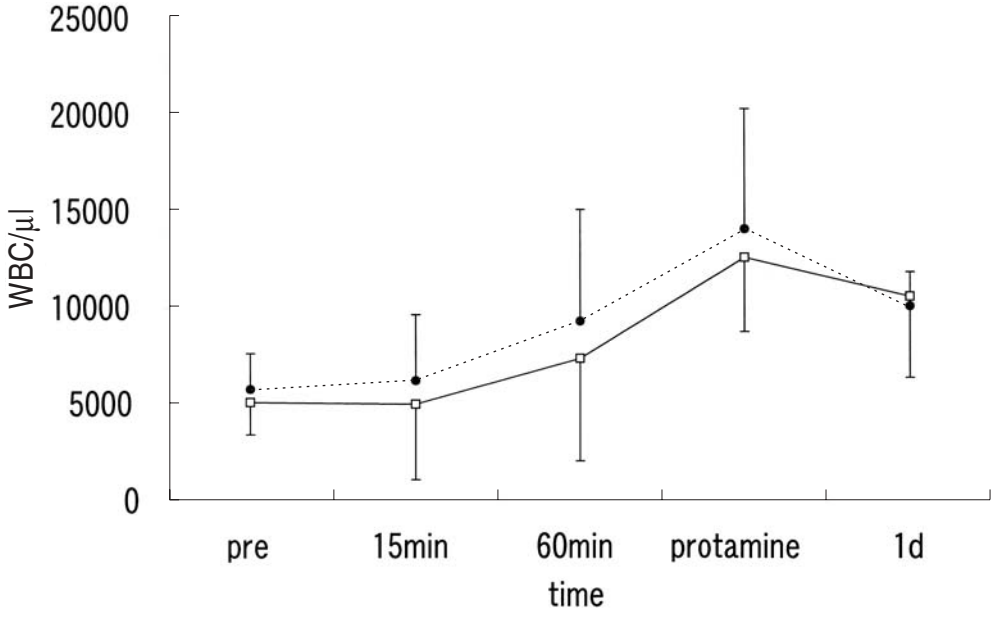

Fig. 1. Comparison of number of white blood cells (*WBC*) in patients with closed circuit (*squares*) and open circuit (*circles*) systems

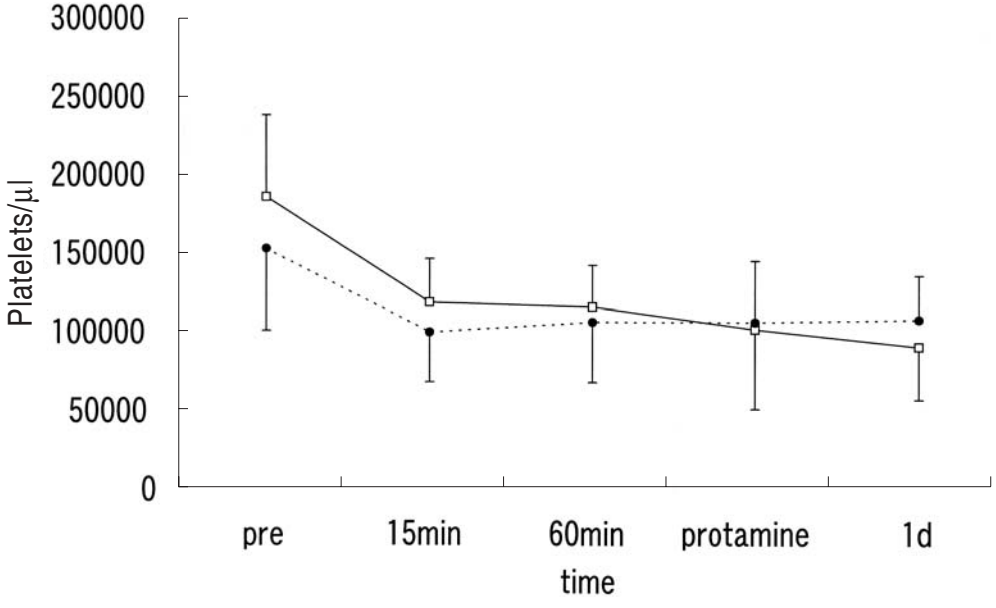

Fig. 2. Comparison of number of platelets in patients with closed circuit and open circuit systems

Thrombin-antithrombin complex

In both groups, TAT increased during CPB and reached a maximum after the injection of protamine (C:109 ± 93, O:85 ± 22 ng/ml). No significant differences were noted between the two groups (Fig. 4).

Plasmin-α2 plasmin inhibitor complex

The pattern of changes in PIC level was almost the same as that for TAT in both groups. The maximum value was reached after the injection of protamine (C:4.8 ± 2.7, O:4.4 ± 1.8 μg/ml). No significant differences between the two groups were noted (Fig. 5).

D-dimer

The pattern of changes in D-dimer level was almost the same as that for TAT in both groups. The maximum level occurred after the protamine injection (C:1.8 ± 1.2, O:2.8 ± 2.5 μg/ml). All values for the closed circuit group were lower than those for the open circuit group, but no significant differences between the two groups were noted (Fig. 6).

Interleukin-6

In both groups, IL-6 increased during CPB. The maximum level occurred after the protamine injection (C:202 ± 110, O:230 ± 146 pg/ml). The changes followed a similar pattern

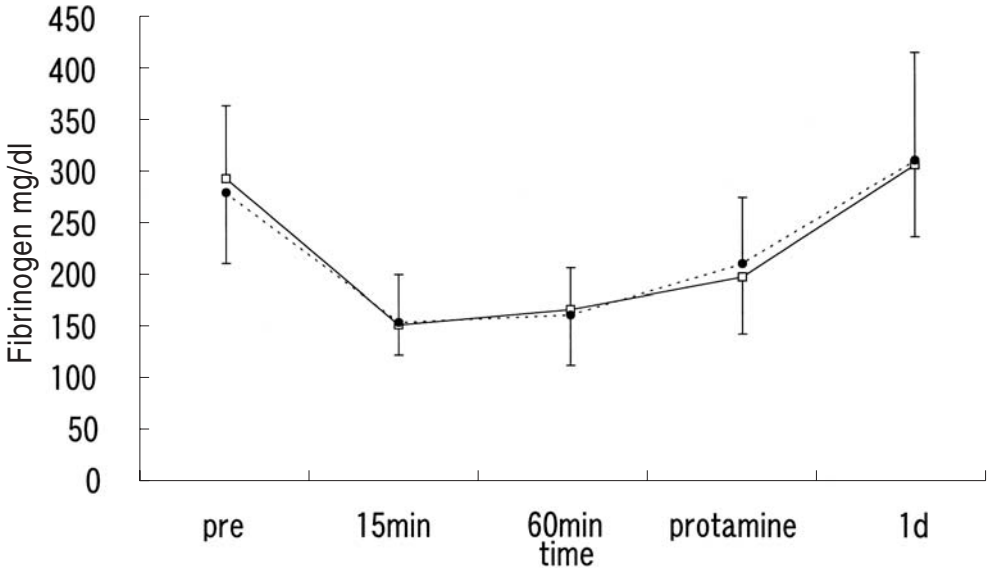

Fig. 3. Comparison of concentration of fibrinogen in patients with closed circuit and open circuit systems

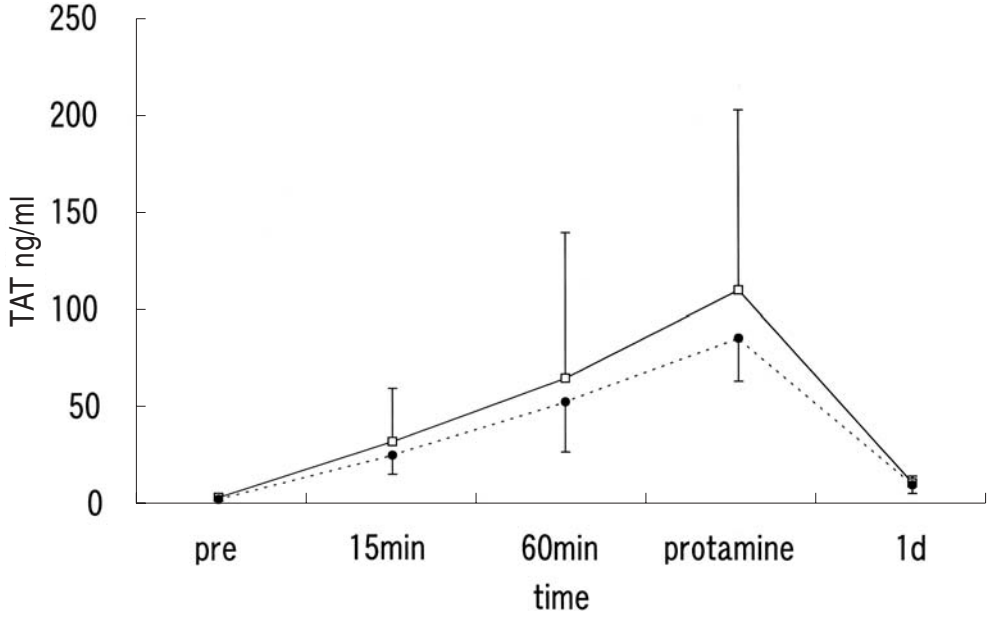

Fig. 4. Comparison of concentrations of thrombin–antithrombin complex (*TAT*) in patients with closed circuit and open circuit systems

to that for TAT. No significant differences were noted (Fig. 7).

Polymorphic neutrophil-elastase

PMN-elastase levels showed an increase similar to that for Il-6 (Fig. 8). The maximum level occurred after the protamine injection (C:551 ± 198, O:571 ± 353 μg/l).

Plasma free hemoglobin

In both groups, plasma free Hb increased during CPB. The maximum level occurred after the protamine injection (C:82.4 ± 47.6, O:94.8 ± 45.3 mg/dl). The value of the closed circuit group at 60 min. after CPB was low, but no significant differences between the two groups were noted (Fig. 9).

Discussion

Contact between blood and circuit surfaces activates the blood in the extracorporeal circulation.[7,8] Therefore, the heparin-coated circuit was developed and the resultant activation of the coagulation system and complement system was reduced.[1–3] The usefulness of the centrifugal pump has also been reported in comparison with the roller pump.[4] To utilize the advantages of the anti-inflammatory and antithrombogenic properties of the heparin-coated circuit and centrifugal pump, a closed circuit that prevents

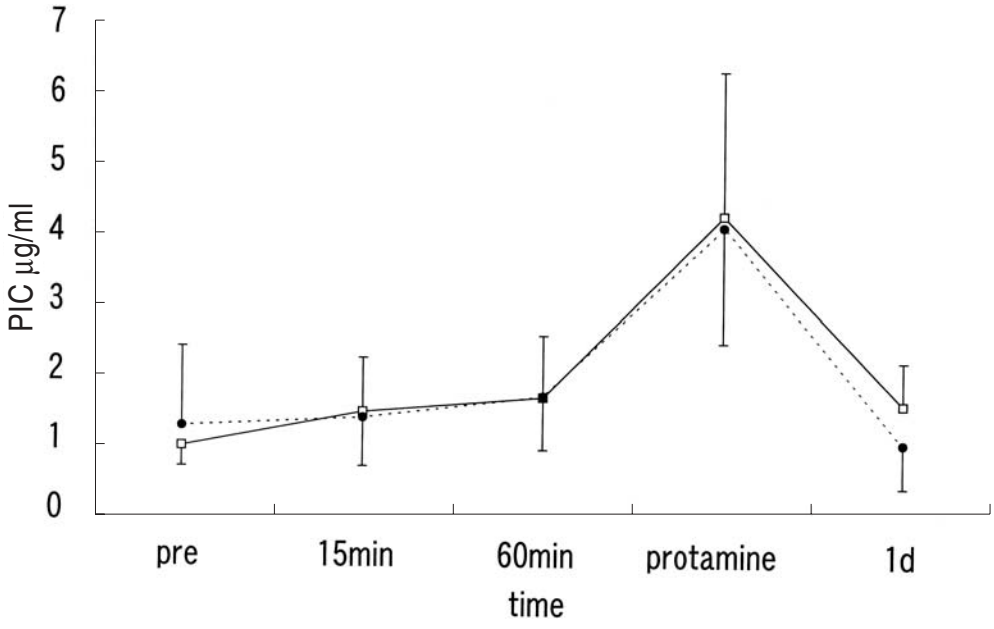

Fig. 5. Comparison of concentration of plasmin-α2 plasmin inhibitor complex (*PIC*) in patients with closed circuit and open circuit systems

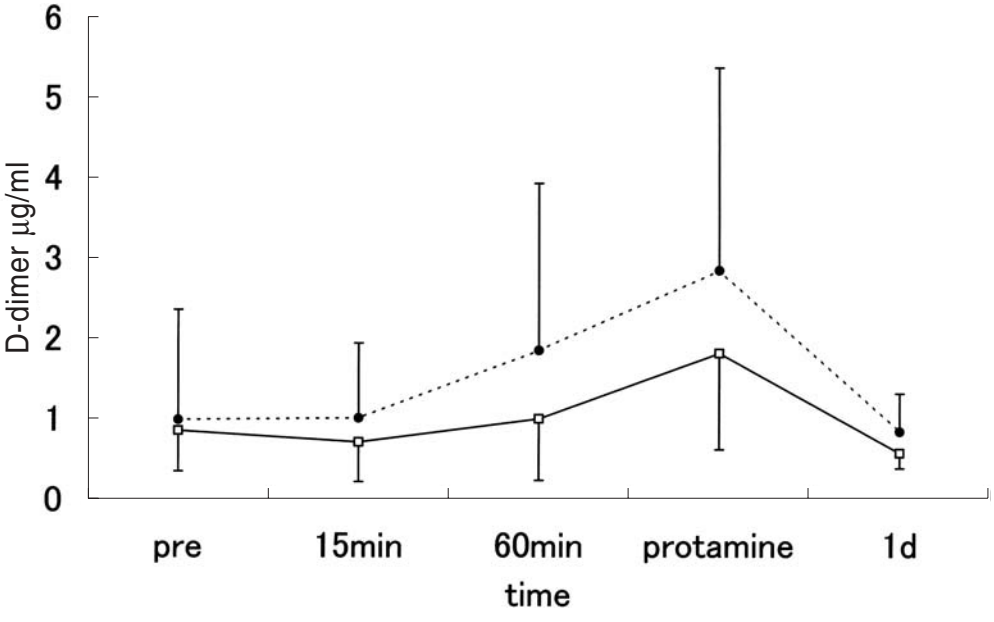

Fig. 6. Comparison of concentration of D-dimer in patients with closed circuit and open circuit systems

contact with the air seems desirable. Higher material-dependent blood activation and acceleration of hemolysis as a result of blood–air contact was reported in CABG operations.[5] The increases in TAT levels were reduced in closed circuit systems during CABG.[9] In in vitro studies, the superiority of the closed circuit has been reported.[6] Air contact was suspected as a cause of the postoperative peak of C3a and elastase in bubble oxygenators.[10] These previous studies were carried out in vitro or during CABG surgery. However, recently CABG is being done without the use of CPB. CBP is more important in valvular heart surgery rather than in ischemic heart surgery. There have been no reports studying the effect of the closed circuit in valvular surgery, so we examined the effect of the closed circuit compared to the open circuit in clinical valvular surgery.

It is reported that the decrease in platelets is prolonged and continues for 3 days after CPB.[11] The elevation in WBC count during CPB was promoted by the mobilization of the peripheral leukocyte pool and mobilization of immature leukocytes to the peripheral blood by bone marrow hyperplasia.[12] Fibrinogen was maintained at a low value by hemodilution in CPB.

In this study, the increase in TAT levels indicated an increase in thrombin even under heparin use; there were no differences between the two systems. To examine fibrinolysis, plasmin-α2 plasmin inhibitor complex (PIC) and D-dimer levels were measured. The increase in PIC levels was much larger than the increase in D-dimer levels. This result indicates that primary fibrinolysis mainly occurred during CPB regardless of whether a closed or open circuit was

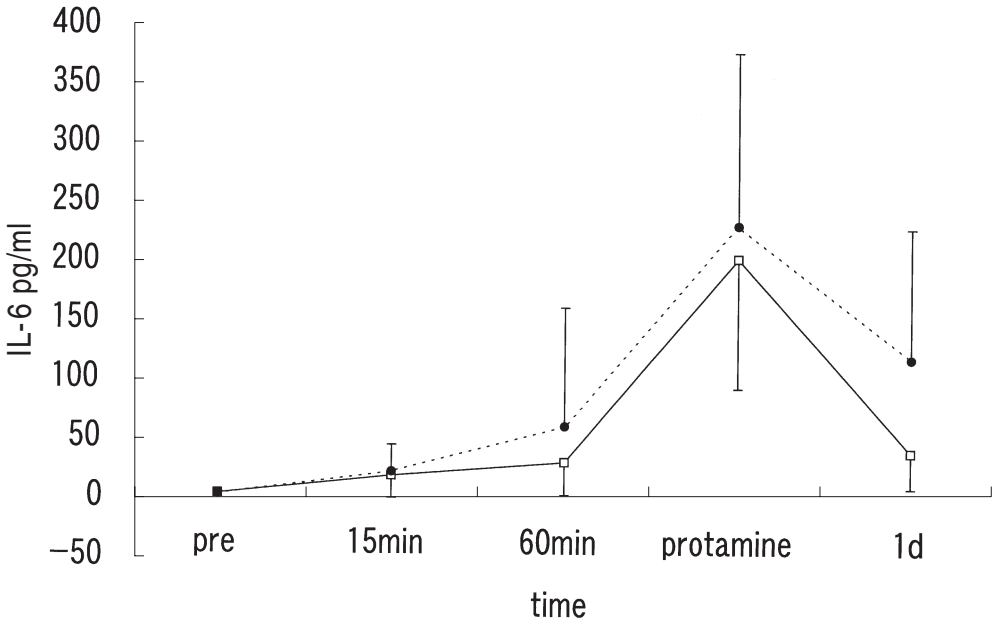

Fig. 7. Comparison of concentration of interleukin 6 (*IL-6*) in patients with closed circuit and open circuit systems

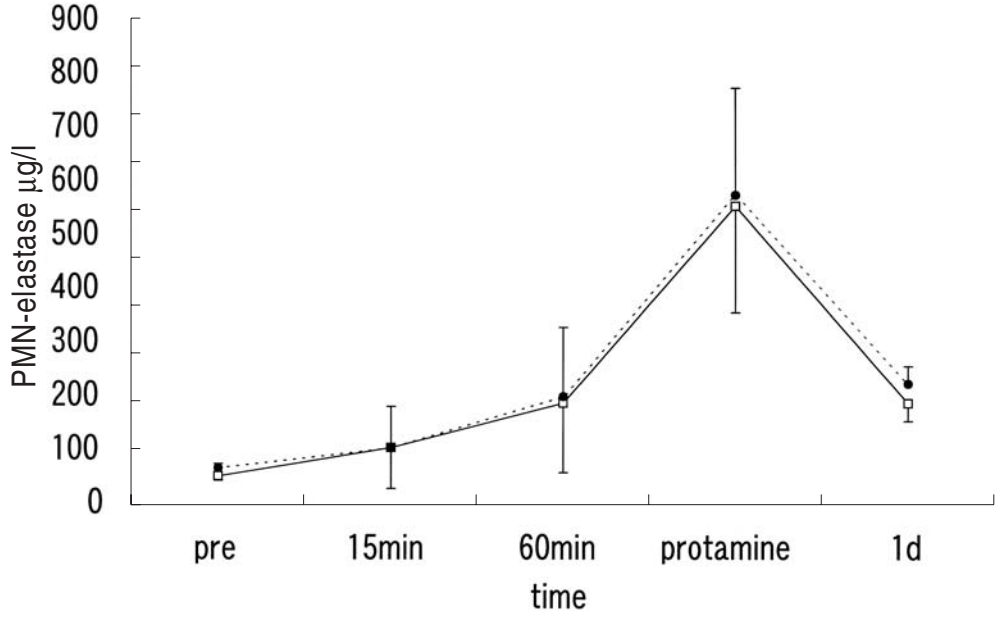

Fig. 8. Comparison of concentration of polymorphic neutrophil-elastase (*PMN-elastase*) in patients with closed circuit and open circuit systems

used. The increases in IL-6 and PMN-elastase levels indicated inflammatory accentuation during CPB and there were no apparent differences in the use of different reservoirs. Plasma free hemoglobin was measured as an index of hemolysis, and no differences were recognized.

In this clinical study, all factors in blood coagulation, fibrinolysis, inflammatory response, and hemolysis were influenced or activated during CPB, and there were no significant differences between the open circuit and closed circuit systems. In the following paragraph we review this result.

Kim et al.[13] reported that the existence of air did not affect the in vitro test of thrombogenicity in mechanical circulatory assist devices. Nishida et al.[6] reported that the closed circuit was useful but that the difference between the open and closed circuits was unexpectedly small. In other words, no significant difference appeared in this clinical study, indicating that any hidden true differences are very small or truly there was no difference. If the difference is small, more complex cardiac surgery or repeat surgery would more likely demonstrate the beneficial effects of the closed circuit.[14] Jensen et al.[15] reported that a heparin-coated CPB system using a centrifugal pump and a closed circuit improves biocompatibility in comparison with the conventional system (uncoated, roller pump, and hard shell reservoir) in pediatric surgery. As in this report, the difference might not be apparent until these extreme settings were undertaken.

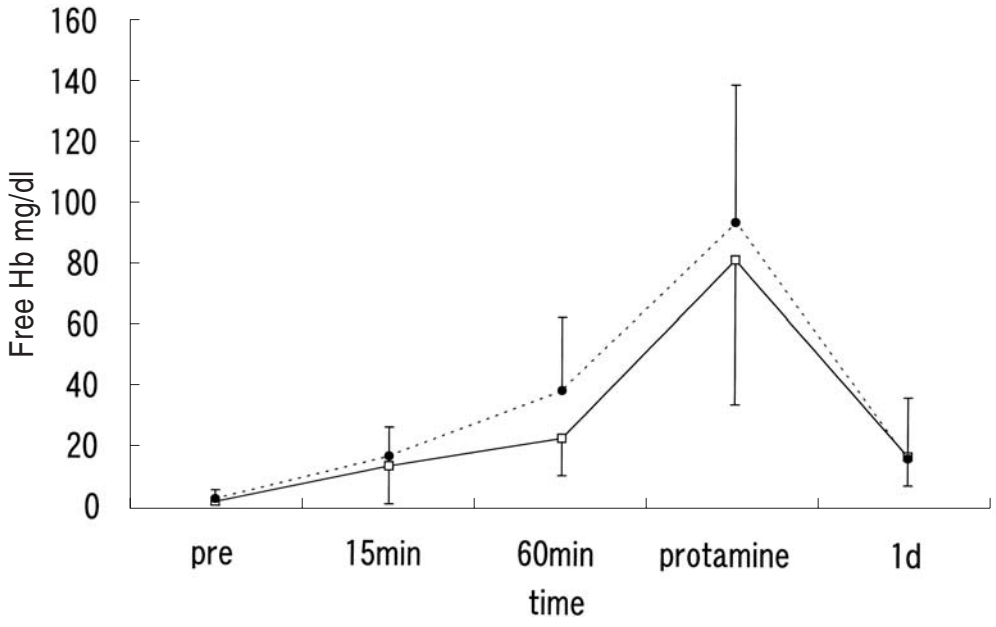

Fig. 9. Comparison of concentration of plasma free hemoglobin (*free Hb*) in patients with closed circuit and open circuit systems

Study limitations

The inherent limitations of this study as summarized as follows:

1. The small sample size was a major study limitation, a larger study should be performed.
2. Another concern is the existence of suction and venting systems, which are indispensable in valvular operations. In the pericardial cavity, tissue factor and tissue-type plasminogen activators accelerate the activation of clotting and consequently of fibrinolysis.[16] In addition cardiotomy suction blood is known to be highly activated.[17] Therefore, minimal suction should be used in the examination of coagulation and fibrinolysis.[5,9] There is a great possibility that the use of the suction and venting systems masked the differences between the open and closed pump circuits.
3. Another factor that influenced this study is the cell saving system. The cell saving system washes out activated proteins, so it could have prevented the deleterious effects of systemic blood activation during the use of the open venous reservoir.[18,19]
4. Finally, systemic heparin levels should be considered. The use of intraoperative systemic heparin is still controversial because heparin itself causes platelet dysfunction and fibrinolysis.[20] There are reports that systemic heparinization can be reduced with the use of a heparin-coated circuit.[21] Improved outcomes have also been reported when a heparin-coated circuit was used in conjunction with reduced systemic heparin.[9] However, Tabuchi et al.[16] reported that appropriate heparin levels to prevent clotting must be maintained because of blood–tissue contact (pericardial cavity), and as long as this occurs, the clotting cascade is still intensively activated. Therefore, we maintained ACT at >400s as Bull reported.[22] Thus, systemic heparin levels might also have affected the results of this study.

Conclusion

Because this study was a clinical analysis, there are many uncertain factors that could have affected this result. No significant differences were evident between the closed circuit and open circuit with a combined heparin-coated system and centrifugal pump in low-risk valvular surgery. Under these circumstances, the choice of closed circuit or open circuit based on biocompatibility might be meaningless. At the moment, clinically, it seems to be appropriate to select either a closed circuit or an open circuit system based on economic efficiency, ease of operation, or safety.

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