Continuous renal replacement therapy with a polymethyl methacrylate membrane hemofilter suppresses inflammation in patients after open-heart surgery with cardiopulmonary bypass

Hiroshi Mukaida, CCP, MS,[1,2] Satoshi Matsushita, MD, PhD,[1*] Takahiro Inotani, CCP,[2] Atsushi Nakamura, PhD,[3] Atsushi Amano MD, PhD[1]

*Corresponding author: Satoshi Matsushita,

Department of Cardiovascular Surgery, Juntendo University Faculty of Medicine,

Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, JAPAN

Email: saty-m@juntendo.ac.jp

Telephone: +81-3-3813-3111

Key words: IL-6, IL-8, postperfusion syndrome, cytokine

The publication is available at www.springerlink.com

ABSTRACT

Background: Cardiopulmonary bypass (CPB) induces a complex inflammatory response involving an increase in inflammatory cytokines, called postperfusion syndrome. Previous studies demonstrated that adsorption of the serum cytokines can reduce acute inflammation and improve clinical outcomes. In this study, patients were placed on continuous renal replacement therapy (CRRT) with a polymethyl methacrylate (PMMA) membrane hemofilter immediately after the start of an open-heart surgery with CPB and throughout the postoperative course to prevent postperfusion syndrome. The aim of this study was to assess whether continuous CRRT using a PMMA filter (PMMA-CRRT) could affect cytokine expression and improve perioperative outcomes.

Methods: We designed a randomized controlled trial, which included 19 consecutive adult patients on maintenance dialysis and 7 consecutive adult patients who were not on maintenance dialysis (NHD group). Patients on maintenance dialysis were randomly divided into 2 groups: 10 patients who received CRRT with a polysulfone membrane hemofilter (PS group) and 9 patients who received CRRT with a PMMA membrane (PMMA group). Blood samples were collected from the radial or brachial artery at 5 different time points.

Results: Comparisons between the PS, PMMA, and NHD groups revealed a significant main effect of time on changes in serum IL-6 and IL-8 concentrations ($p < 0.01$) and an interaction ($p < 0.05$) between time and group. Plasma IL-6 and IL-8 levels after surgery were significantly lower in the PMMA group than in the PS group, while other cytokines measured in this study were not significantly different. In addition, clinical outcomes were not significantly different between the groups.

Conclusions: The continuous use of PMMA-CRRT throughout the perioperative period suppressed serum IL-6 and IL-8 concentrations, although there were no differences in clinical outcomes.

Introduction

Cardiopulmonary bypass (CPB) induces a complex inflammatory response that has a multifactorial pathogenesis. The inflammatory response is triggered by exposure of the blood to artificial surfaces during extracorporeal circulation, ischemia/reperfusion injuries, and translocation of gram-negative bacteria from the intestinal tract. The inflammatory response is a result of complement, neutrophil, and macrophage activation, and the release of the inflammation-related cytokines, e.g. interleukin-6 (IL-6) or IL-8[1−3]. CPB-induced immune system activation can lead to systemic inflammatory response syndrome (SIRS) [4,5]. The combination of inflammatory injury and inadequate perfusion to end-organs can lead to tissue damage and dysfunction of multiple internal organs by a phenomenon called postperfusion syndrome [6–8]. Although the postperfusion syndrome is rare, it has a mortality rate of more than 50% [9], making it a serious risk in CPB; therefore, a protective strategy for postperfusion syndrome is important [10–12]. Furthermore, the damage is likely to be more severe when serum inflammatory cytokine levels are high, especially in the case of patients with chronic renal failure[13,14].

Extensive research has been conducted to determine methods to reduce these injuries in clinical practice. Some of these methods include decreasing the extent of exposure of blood to artificial surfaces[15] and prolonged inhibition of fibrinolysis by administering an additional postoperative dose of tranexamic acid to CPB patients[16], which might indirectly decrease the postoperative inflammatory response. Although methods to directly reduce the inflammatory response through the use of a leukocyte removal filter and endotoxin adsorption column have been proposed, there is no clear consensus on an effective method[17,18].

It has been reported that continuous renal replacement therapy (CRRT) with a polymethyl methacrylate (PMMA) membrane hemofilter, which adsorbs IL-6, improved the

hemodynamics and prognosis of sepsis patients, in whom the concentration of serum IL-6 is known to be strongly correlated with disease severity. IL-6 is known to cause significant myocardial depression in vitro, and it has been shown to be a myocardial depressant factor (MDF), which aids the progression of hemodynamic instability. Furthermore, studies have reported that the removal of IL-6 from the serum restores myocardial contractility[19,20]. These findings suggest that there are clinical benefits to the removal of IL-6 from the serum. In addition to indirect treatment methods that prevent the onset of inflammation, direct treatment methods, such as those that control IL-6 levels, can be used in future treatment strategies. Therefore, in this study, we placed patients on CRRT with a PMMA membrane hemofilter (PMMA-CRRT) immediately after the start of an open-heart surgery with CPB and throughout the postoperative course to assess whether the continuous PMMA-CRRT led to a reduction in inflammation-related cytokines levels including IL-6, and improved perioperative outcomes, thereby preventing postperfusion syndrome.

Materials and methods

Subjects

We designed a randomized controlled trial, which included 19 consecutive adult patients on maintenance dialysis and 7 consecutive adult patients who were not on maintenance dialysis; all patients were undergoing elective valvuloplasty or valve replacement with CPB at Juntendo University Hospital from January 2014 to October 2014. Prior to surgery, written informed consent was obtained from patients according to a protocol approved by the internal review committee on Ethics of Human Investigation of the Juntendo University Hospital. Patients who underwent on-pump beating surgery, had circulatory arrest, and were operated on as emergency cases were excluded from the study. This study was approved by our institutional review board, and written informed consent was obtained from all patients. The patients on maintenance dialysis were randomly divided into 2 groups: patients who received CRRT with a polysulfone membrane hemofilter (10 patients; PS group) and patients who received CRRT with a PMMA membrane hemofilter (9 patients; PMMA group). The 7 patients who were not on maintenance dialysis were recruited as the control group (NHD group).

Anesthesia

None of the patients received premedication. All patients underwent general anesthesia. While the patients were under anesthesia, electrocardiography and transesophageal echocardiography were performed, and arterial pressure, central venous pressure, pulmonary artery pressure, arterial oxygen saturation (SpO_2), end-tidal CO_2 tension, rectal temperature, and urine output were monitored. Arterial blood gas analysis was performed intermittently. General anesthesia was induced by administering midazolam and fentanyl. Orotracheal intubation was facilitated with rocuronium. Anesthesia was maintained with sevoflurane,

propofol, and remifentanil. After the surgery, all patients were transferred to the intensive care unit (ICU) under sedation with propofol.

The CPB and CRRT procedures

The CPB parameters were as follows: perfusion index, 2.6 L/min/m^2; venous oxygen saturation (SvO_2), > 65%; and venous oxygen tension (PvO_2), > 45 mmHg. The technique used for myocardial protection was identical in all patients. Intermittent tepid blood cardioplegia was prepared by mixing oxygenated blood with Miotector (Mochida, Pharmaceutical Co. Ltd., Tokyo) and was administered in an antegrade fashion into the aortic root and in a retrograde fashion into the coronary sinus. Immediately after beginning the surgery, a vascular access catheter (Blood Access UK-Catheter KIT, UB-1120-W, NIPRO, Osaka) was placed into the right femoral vein to initiate CRRT in the PS group (EXCELFLO, AEF-10, Asahikasei Medical, Tokyo) and PMMA group (HEMOFEEL, CH-1.8W, Toray Medical, Tokyo). CRRT was performed before and after CPB under the following conditions: blood flow rate (Q_B) = 80–100 mL/min, dialysate flow rate (Q_F) = 10–15 mL/kg/h, and filtration rate (Q_D) = 10–15 mL/kg/h. The CRRT conditions during CPB were adjusted as follows: Q_B = 200–250 mL/min, Q_D = 40–50 mL/kg/h, and Q_F = 40–50 mL/kg/h, while vascular access was not changed. Nafamostat mesilate (20–30 mg/h) was infused for anticoagulation. The hemodiafiltration system was monitored via a personal bedside console (ACH-Σ, Asahikasei Medical, Tokyo), and the hemofilters were not changed from the time CRRT was started until 12 h after the surgery.

Measurements

Blood samples were collected from the radial or brachial artery at five different time points: after induction of anesthesia; after CPB; and at 0 h, 6 h, and 12 h after admission to the ICU. Arterial blood gas analysis (RAPID Lab 1245, Siemens, Germany) was performed. We documented hemodynamic parameters and postoperative fluid balance for 12 hours post-

operatively. The cardiac index was monitored by using a continuous hemodynamic monitoring system (Vigilance II, Edwards Lifesciences, CA). The systemic vascular resistance index (SVRI) was calculated by using the following equation: SVRI = 79.92 × (mean arterial pressure – mean right atrium pressure)/cardiac index. The PaO_2/FiO_2 ratio and oxygenation index (OI = [mean airway pressure × FiO_2 × 100]/PaO_2) were evaluated as marker of pulmonary function. Blood samples were centrifuged, and the plasma was frozen and stored until the cytokine analysis. Serum IL-1β, IL-2, IL-6, IL-8, IL-10, IL-17, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) levels were measured using an enzyme-linked immunosorbent assay (Bio-Plex200, Bio-Rad Laboratories Inc, CA). As indicators of clinical outcome, intubation time, duration of ICU stay, duration of postoperative hospital stay, new onset of postoperative atrial fibrillation, postoperative stroke, and hospital mortality were assessed.

Statistical analysis

Measurements were presented as the mean ± standard deviation or a median (quartiles). Changes in the serum concentration of the cytokines at the 5 different measurement points as compared to the concentration after the induction of anesthesia (reference value) were calculated. The statistical analysis involved comparing these values between the NHD, PS and PMMA groups. The mixed-effects model, that takes into account the random effects of individual differences, was used to analyze longitudinal data between the three groups. Measurement data were further compared by using Welch's t-test, Mann-Whitney *U* test or Tukey's honestly significant difference test, which is used to compare clinical variables. All values were calculated and analyzed by using a computer statistical software program (JMP12, SAS Institute Inc. NC). Statistical significance was defined as a p value of less than 0.05.

Results

Patients' background

Characteristics of patient are summarized in Table 1. There were no differences in mean age, gender, preoperative NYHA classification and European System for Cardiac Operative Risk Evaluation (EuroSCORE) between the groups. Body surface area was significantly higher in the PMMA group than in the PS group ($p < 0.05$). There was no significant difference in length of time on dialysis between the PS and PMMA groups. The preoperative value of serum BNP was the highest in the PMMA group and the lowest in the NHD group. Each of the recorded values were significantly higher in the PS and PMMA groups than in the NHD group ($p < 0.01$, respectively), while there was no statistical difference between the PS and PMMA groups. In this study period, we enrolled patients who underwent either aortic valve replacement, mitral valvuloplasty, or both. In studying both, we found no difference in the procedures between groups. Furthermore, although each of the CPB time and aortic cross-clamping time tended to be longer in the NHD group, there were no differences between each group.

Cytokine Measurements

The time course change in serum cytokine levels is shown in Fig. Comparison between the PS, PMMA, and NHD groups revealed that the "main effect of time" on changes in concentrations of serum IL-6, IL-8, and IL-17 were significantly different ($p < 0.01$, each). The changes in plasma IL-6 and IL-8 concentrations were significantly greater ($p < 0.05$, each) in the PS group than in the PMMA group ("group and time interaction" in Fig). In addition, the plasma IL-6 and IL-8 levels after surgery (at the time of admission to the ICU) were significantly lower in the PMMA group than in the PS group (IL-6: 292.8 ± 150.0 vs. 616.2 ± 499.1 pg/mL, $p < 0.05$; IL-8: 54.7 ± 37.2 vs. 154.3 ± 156.9 pg/mL; $p < 0.05$). The other cytokines measured in this study (IL-1β, IL-2, IL-10, IFN-γ, and TNF-α) were not

statistically different between each group. Notably, the IL-1β and IFN-γ levels were the highest upon admission to the ICU, although there was no difference between each group (IL-1β: 1.29 ± 1.29 vs. 0.20 ± 2.14 vs. 0.10 ± 0.28 pg/mL, IFN-γ: 239.1 ± 322.4 vs. 93.0 ± 156.7 vs. 52.8 ± 149.8 pg/mL, in PS vs. PMMA vs. NHD, respectively).

Clinical outcomes

The clinical outcomes were compared between the three groups (Table 2). Intubation time was the shortest in the NHD group, although it was not statistically different between each group. The duration of the ICU stay was significantly shorter in the NHD group than in the PS and PMMA groups. The postoperative hospital stay was not statistically different between each group, although it tended to be shorter in the PMMA group than in the PS group. There was no difference in the new onset of postoperative AF. In addition, no postoperative stroke was observed to have occurred in any group. Although one case of mortality was documented in the PMMA group due to ventricular fibrillation, there was no significant difference in mortality between the groups.

The post-operative fluid balance within 12 h of ICU administration was lower in the PMMA group compared to the PS group, although there was no significant difference between each group. Furthermore, the PF ratio was higher and the OI was lower in the PMMA group compared to the PS group at the time of ICU administration, although there were no significant differences between each group. In addition, the cardiac index and SVRI were the same in each group.

Discussion

In the present study, we observed that the inflammatory response following CPB was enhanced in the maintenance hemodialysis patients compared to the NHD patients. Furthermore, the reduction in serum IL-6 and IL-8 levels was significantly greater following the use of a PMMA membrane compared to a PS membrane.

Inflammatory response in hemodialysis patients

CPB is an essential cardiac surgery procedure, and it is known to induce inflammation-related cytokines, including IL-6 and IL-8[1–3]. In addition, previous reports have shown that maintenance hemodialysis is also a cause of chronic inflammation[21], along with malnutrition and atherosclerosis, which collectively are termed as the malnutrition, inflammation, and atherosclerosis (MIA) syndrome[13]. Since the kidneys play an important role in the metabolism of advanced glycation end products, which induce the release of inflammatory cytokines[22], renal function impairment leads to an increase in those cytokines in maintenance hemodialysis patients[23]. Therefore, it is expected that the inflammatory response will be prominent in chronic dialysis patients undergoing CPB as these patients are more sensitive and prone to inflammatory changes.

Protective strategies for postperfusion syndrome

The combination of inflammatory injury and inadequate perfusion to end-organs can lead to tissue damage and dysfunction of multiple internal organs by a phenomenon called postperfusion syndrome. Although postperfusion syndrome rarely occurs, it has a mortality rate of more than 50% [9], making it a serious risk in CPB. Thus, anti-inflammatory therapy should be considered to suppress the inflammatory response that causes postperfusion syndrome. In fact, increased IL-6 levels at the end of CPB are correlated with reduction in postoperative respiratory function [24]. In this study, PMMA-CRRT, which has high IL-6 adsorption properties, was evaluated as an anti-inflammatory therapy. Although post-

surgical plasma IL-6 levels were significantly lower in the PMMA group than in the PS group, there were no differences in respiratory function between these groups. However, as described above, as PMMA-CRRT can suppress IL-6 levels, it may reduce the risk for postperfusion syndrome.

Adsorption of IL-6 by the PMMA membrane

We demonstrated that PMMA-CRRT, which has a high IL-6 adsorption property, expecting to attenuate the CPB-induced IL-6 increase as compared to CRRT with a regular (PS) membrane hemofilter (PS-CRRT). The use of CRRT for the removal of cytokines was first reported in 1992[25]. Although a blood filtration method can be used to filter cytokines non-specifically, the removal of cytokines that have a molecular weight of 20 kDa or larger is not recommended as it can lead to the removal of albumin. Because blood is diluted during CPB, blood filtration using a high cut-off hemofilter with a large pore size could lead to albumin loss and is therefore not preferable. In this study, we used an adsorption method for cytokine removal, and PMMA membranes have a larger surface area (1.8 m^2) and are more effective in adsorbing IL-6[26]. PMMA-CRRT is commonly used for cytokine removal in sepsis patients, and it has been reported to significantly decrease plasma IL-6 concentrations, decrease catecholamine dose, and improve mortality rates[27,28]. Researchers have previously reported that IL-6 is a MDF in meningococcal disease. Further, it has been shown that the adsorption of IL-6 diminished the serum myocardial depressant activity of patients with meningococcemia, and IL-6 concentrations correlated with clinical disease severity[19,20]. These findings support the notion that IL-6 plays an important role in cause of postperfusion syndrome and could therefore be a therapeutic target in patients who undergo open-heart surgery with CPB.

Clinical relevance of reduction in serum IL-8

It has been known that respiratory dysfunction in patients with acute kidney injury, which is a component of postperfusion syndrome, is associated with vascular permeability that is facilitated by increase of IL-8[29]. Some reports have suggested that CRRT can control the systemic inflammation induced by venovenous extracorporeal membrane oxygenation in a porcine model[30,31]. In these studies, although either PS or polyacrylonitrile membrane hemofilters were used, CRRT suppressed the increase in inflammatory cytokine concentrations in the blood as well as in bronchoalveolar lavage fluids and also protected the lung parenchyma from the adverse effects of extracorporeal membrane oxygenation[31]. We found that PMMA-CRRT significantly attenuated the increase in serum IL-8 compared to PS-CRRT patients. Although there was no statistical significance in the factors measured in this study, PMMA showed a trend of requiring a shorter intubation time, less fluid balance, higher PF ratio, and lower OI compared to PS. These results suggest that the reduction of IL-8 may provide significant benefit for patients with lung complications or more severe conditions.

Clinical benefits in early induction of CRRT

In this study, we induced CRRT therapy during surgery in an attempt to remove the inflammatory-related cytokines as much as possible. In fact, all patients were easily weaned off CPB and none required treatment for major central nervous system disorders or organ dysfunction after the open-heart surgery with CPB, even though we attempted to maintain hemodynamic stability by administering inotropic and vasoconstrictor agents throughout the surgery. In a prospective multicenter observational study on the initiation timing of renal replacement therapy (RRT), early RRT resulted in improvements in the survival of postcardiotomy patients with acute renal failure, whereas late RRT was associated with a longer RRT duration, longer hospital stay, and higher mortality[32,33]. However, early

CRRT, which helps maintain control of the fluid balance, may have led to the inhibition of cytokines that could affect patient outcomes in these reports.

Limitations

Our study has several limitations. The sample size may be insufficient to evaluate effective inhibition. Moreover, the cytokine decrease achieved with the blood purification procedures used in this study may be ascribed to the blood purification settings used, such as Q_B, Q_F, and Q_D; the hemofilter membrane matrix; and the differences in used filter surface area. Therefore, cytokine clearance should have been calculated in order to accurately evaluate cytokine removal.

Conclusions

Our study suggests that PMMA-CRRT immediately after the start of an open-heart surgery with CPB and throughout the postoperative course is effective in inhibiting the increase in inflammatory-related cytokines and may improve postoperative outcomes in adult maintenance hemodialysis patients who undergo open-heart surgery with CPB.

Funding. – This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest. – The authors have no conflicts of interest to declare.

Acknowledgements. – We thank all the staff for their assistance in conducting this study. This research received no specific grants from any funding agency in the public, commercial,or not-for-profit sectors.

Figure captions:

Fig. Changes in serum IL-1β (a), IL-2 (b), IL-6 (c), IL-8 (d), IL-10 (e), IL-17 (f), IFN-γ (g), and TNF-α (h) concentrations (at each measurement point – baseline) during the perioperative period across the three groups. The main effect of time was significant ($p < 0.01$) for IL-6 (c), IL-8 (d), and IL-17 (f). There was an interaction ($p < 0.05$) between time and group for IL-6 (c) and IL-8 (d)

REFERENCES

1. Westaby S. Organ dysfunction after cardiopulmonary bypass. A systemic inflammatory reaction initiated by the extracorporeal circuit. *Intensive Care Med*. 1987; 13(2): 89–95.

2. Kawamura T, Wakusawa R, Okada K, Inada S. Evaluations of cytokines during open heart surgery with cardiopulmonary bypass: participation of interleukin 8 and 6 in reperfusion injury. *Can J Anaesth.* 1993; 40: 1016–21.

3. Sawa Y, Shimazaki Y, Kadoba K, Masai T, Fukuda H, Ohata T, et al. Attenuation of cardiopulmonary bypass derived inflammatory reactions reduces myocardial reperfusion injury in open heart surgery. *J Thorac Cardiovasc Surg.* 1996; 111: 29–35.

4. Engels M, Bilgic E, Pinto A, Vasquez E, Wollschläger L, Steinbrenner H, et al. A cardiopulmonary bypass with deep hypothermic circulatory arrest rat model for the investigation of the systemic inflammation response and induced organ damage. *J Inflamm.* 2014 Aug 12; 11: 26.

5. Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Miyazaki M. Immunosuppression following surgical and traumatic injury. *Surg Today*. 2010, 40(9): 793-808.

6. Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest.* 1997; 112: 676-92.

7. Moat NE, Shore DF, Evans TW. Organ dysfunction and cardiopulmonary bypass: the role of complement and complement regulatory proteins. *Eur J Cardiothorac Surg.* 1993; 7: 563–73.

8. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1983; 86: 845–57.

9. Steinberg J, Fink G, Picone A, Searles B, Schiller H, Lee HM, et al. Evidence of increased matrix metalloproteinase-9 concentration in patients following cardiopulmonary bypass. *J Extra Corpor Technol.* 2001 Dec;33(4): 218-22.

10. Prasad A, Stone GW, Holmes DR, Gersh B. Reperfusion injury, microvascular dysfunction, and cardioprotection: the dark side of reperfusion. *Circulation*. 2009; 120(21): 2105-2112.

11. Sanada S, Komuro I, Kitakaze M. Pathophysiology of myocardial reperfusion injury: preconditioning, postconditioning, and translational aspects of protective measures. *Am J Physiol Heart Circ Physiol.* 2011, 301(5): H1723-H1741.

12. Maganti M, Badiwala M, Sheikh A, Scully H, Feindel C, David TE, et al. Predictors of low cardiac output syndrome after isolated mitral valve surgery. *J Thorac Cardiovasc Surg.* 2010; 140(4): 790-796.

13. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation, and atherosclerosis (MIA syndrome). *Nephrol. Dial. Transplant*. 2000; 15: 953-960.

14. Herbelin A, Ureña P, Nguyen AT, Zingraff J, Descamps-Latscha B. Elevated circulating levels of interleukin-6 in patients with chronic renal failure. *Kidney Int.* 1991 May; 39(5): 954-60.

15. Shann KG, Likosky DS, Murkin JM, Baker RA, Baribeau YR, DeFoe GR, et al. An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. *J Thorac Cardiovasc Surg.* 2006; Aug; 132(2): 283-90.

16. Jiménez JJ, Iribarren JL, Brouard M, Hernández D, Palmero S, Jiménez A, et al. Safety and Effectiveness of two treatment regimes with tranexamic acid to minimize inflammatory

response in elective cardiopulmonary bypass patients: a randomized double-blind, dosedependent, phase IV clinical trial. *J Cardiothorac Surg.* 2011 Oct 14; 6: 138

17. Zhang X, Zhou C, Zhuang J, Xiao X, Zheng S, Xiong W, et al. Effects of leukocyte depletion on cardiopulmonary protection and inflammation after valve surgery. *Int J Artif Organs.* 2010; Nov33(11): 812-8.

18. Blomquist S, Gustafsson V, Manolopoulos T, Pierre L. Clinical experience with a novel endotoxin adsorbtion device in patients undergoing cardiac surgery. *Perfusion.* 2009 Jan; 24(1): 13-7.

19. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. *Lancet.* 2004 Jan 17; 363(9404): 203-9.

20. Pathan N, Franklin JL, Eleftherohorinou H, Wright VJ, Hemingway CA, Waddell SJ, et al. Myocardial depressant effects of interleukin 6 in meningococcal sepsis are regulated by p38 mitogen-activated protein kinase. *Crit Care Med.* 2011 Jul; 39(7): 1692-711.

21. Stefoni S, La Manna G, Zanchelli F, Dalmastri V, Perna C, Pace G, et al. Clinical biology of artificial organ substitution. *Nephrol Dial Transplant.* 1998; 13 Suppl 7: 51-4.

22. Heidland A, Sebekova K, Schinzel R. Advanced glycation end products and the progressive course of renal disease. *Am J Kidney Dis.* 2001; 38: S100-S106.

23. Panihi V, Miglion M, De Pietro S, Taccola D, Bianchi AM, Giovannini L, et al. C-reactive protein and interleukin-6 level are related to renal function in predialytic chronic renal failure. *Nephron.* 2002; 91: 594-600.

24. Halter J, Steinberg J, Fink G, Lutz C, Picone A, Maybury R, et al. Evidence of systemic cytokine release in patients undergoing cardiopulmonary bypass. *J Extra Corpor Technol*. 2005 Sep;37(3): 272-7.

25. Bellomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit Care Med.* 1993; 21: 522-26.

26. Hirayama Y, Oda S, Tateishi Y, Sadahiro T, Nakamura M, Watanabe E, et al. Comparison of interleukin-6 removal properties among hemofilters consisting of varying membrane materials and surface areas: An in vitro study. *Blood Purif.* 2011; 31: 18-25.

27. Nakada T, Oda S, Hirosawa H, Sadahiro T, Nakamura M, Abe R, et al. Continuous hemodiafiltration with PMMA hemofilter in the treatment of patients with septic shock. *Mol Med.* 2008; 14: 257-263.

28. Matsuda K, Moriguchi T, Harii N, Goto J. Comparison of efficacy between continuous hemodiafiltration with a PMMA membrane hemofilter and a PAN membrane hemofilter in the treatment of a patient with septic acute renal failure. *Transfusion Apher Sci.* 2009; 40: 49-53.

29. Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol*. 2016 Jan;12(1):48-60.

30. Yimin H, Wenkui Y, Jialiang S, Qiyi C, Juanhong S, Zhiliang L, et al. Effects of continuous renal replacement therapy on renal inflammatory cytokines during extracorporeal membrane oxygenation in a porcine model. *J Cardiothorac Surg.* 2013 Apr 29; 8: 113.

31. Shi J, Chen Q, Yu W, Shen J, Gong J, He C, et al. Continuous renal replacement therapy reduces the systemic and pulmonary inflammation induced by venovenous extracorporeal membrane oxygenation in a porcine model. *Artif Organs.* 2014 Mar; 38(3): 215-23.

32. Liu KD, Himmelfarb J, Paganini E, Ikizler TA, Soroko SH, Mehta RL, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol.* 2006 Sep; 1(5): 915-9.

33. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J Crit Care.* 2009 Mar; 24(1): 129-40.

Table 1. Comparison of clinical backgrounds among the three groups

	PS	PMMA	NHD
Number of the patients	10	9	7
Age, *years*	68.5 ± 10.2	71.8 ± 8.0	72.8 ± 5.5
Female (%)	5 (50.0)	2 (22.8)	3 (42.9)
BSA, m^2	1.44 ± 0.18†	1.61 ± 0.10	1.57 ± 0.25
Length of time on dialysis, *years*	12.4 ± 7.3	10.2 ± 8.2	N/A
LVEF, *%*	64.9 ± 7.4	57.3 ± 12	67.6 ± 5.6
NYHA	2.0 ± 0.47	1.7 ± 0.7	2.4 ± 1.1
Euro SCORE	6.2 ± 4.3	4.2 ± 2.6	3.7 ± 2.5
BNP, *pg/mL*	544 (174–1897)*	1235 (351–2161)*	66 (26–162)
Surgical Procedure			
AVR (%)	5 (50.0)	6 (66.7)	3 (42.9)
MVP (%)	2 (20.0)	1 (11.1)	1 (14.3)
AVR+MVP (%)	3 (30.0)	2 (22.2)	3 (42.9)
CPB time, *min*	135 ± 27	141 ± 36	169 ± 57
Aortic cross-clamping time, *min*	112 ± 27	113 ± 32	139 ± 56
Operation time, *min*	293 ± 74	252 ± 107	293 ± 108

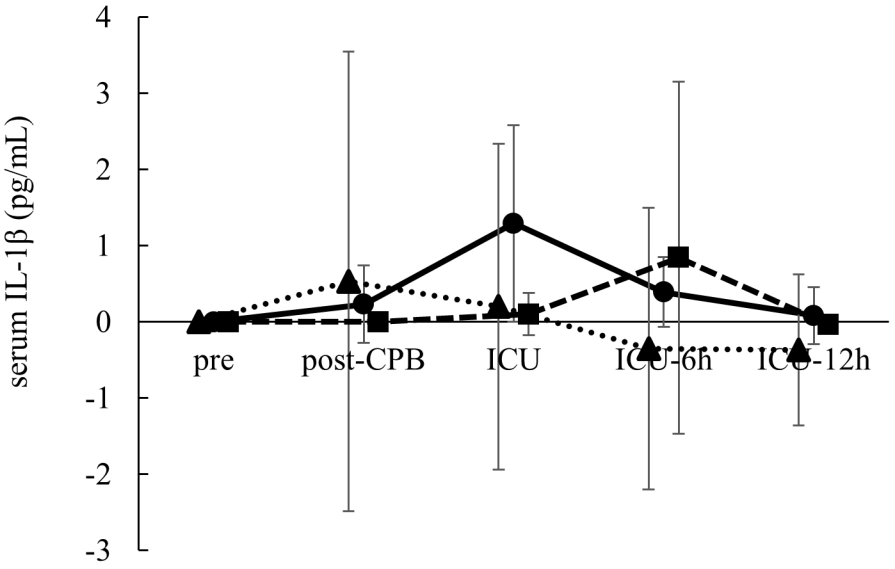
Data were expressed as mean ± SD, median (quartiles) or numbers. BSA: body surface area, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association grading, BNP: brain natriuretic peptide, AVR: aortic valve replacement, MVP: mitral valvuloplasty, CPB: Cardiopulmonary bypass. († $p < 0.05$ PS vs PMMA, *$p < 0.01$ vs NHD)

Table 2. Comparison of clinical outcomes among the three groups

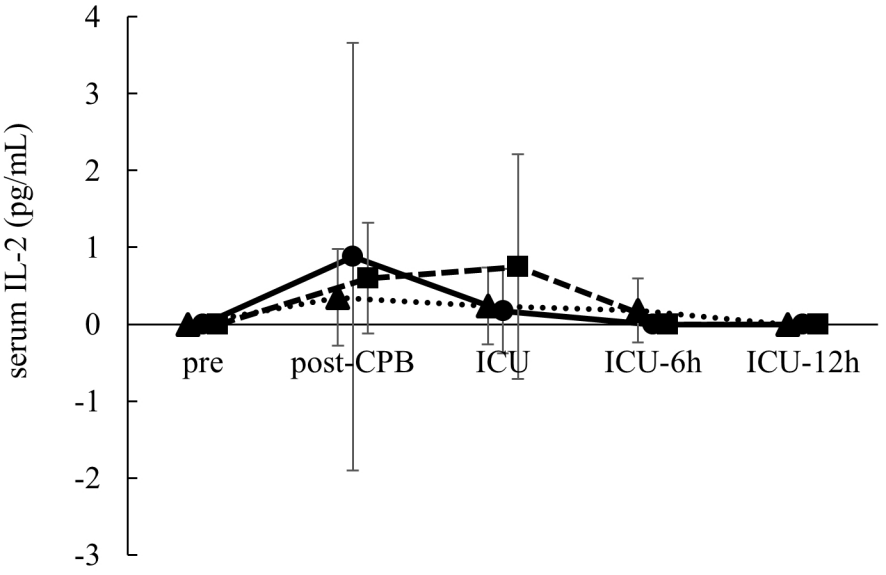
	PS	PMMA	NHD
Intubation time, *min*	691 ± 409	625 ± 303	456 ± 187
ICU stay, *day*	4.5 ± 0.3*	4.1 ± 0.2*	2.5 ± 0.7
Postoperative hospital stay, *day*	18.5 ± 10.2	17.1 ± 5.6	17.4 ± 7.6
Postoperative atrial fibrillation (%)	3 (30.0)	2 (22.2)	0 (0.0)
Postoperative stroke (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hospital mortality (%)	0 (0.0)	1 (11.1)	0 (0.0)
Postoperative fluid balance (12 h), *mL*	340 ± 1024	-90 ± 474	-26 ± 1025
Cardiac index at ICU (0 h), $L/min/m^2$	2.55 ± 0.68	2.28 ± 0.66	2.67 ± 0.92
SVRI at ICU (0 h), $dynes \times sec/cm^5 \times m^2$	2588 ± 775	2353 ± 591	2045 ± 611
PF at ICU (0 h), *kPa*	41.5 ± 10.5	47.1 ± 8.4	40.7 ± 10.5
OI at ICU (0 h), cmH_2O/kPa	27.6 ± 9.2	18.8 ± 5.2	23.6 ± 6.6

ICU: Intensive care unit, OI: oxygenation index, PF: PaO_2/FiO_2 ratio, SVRI: Systemic vascular resistance index.
(* $p < 0.05$ vs NHD)

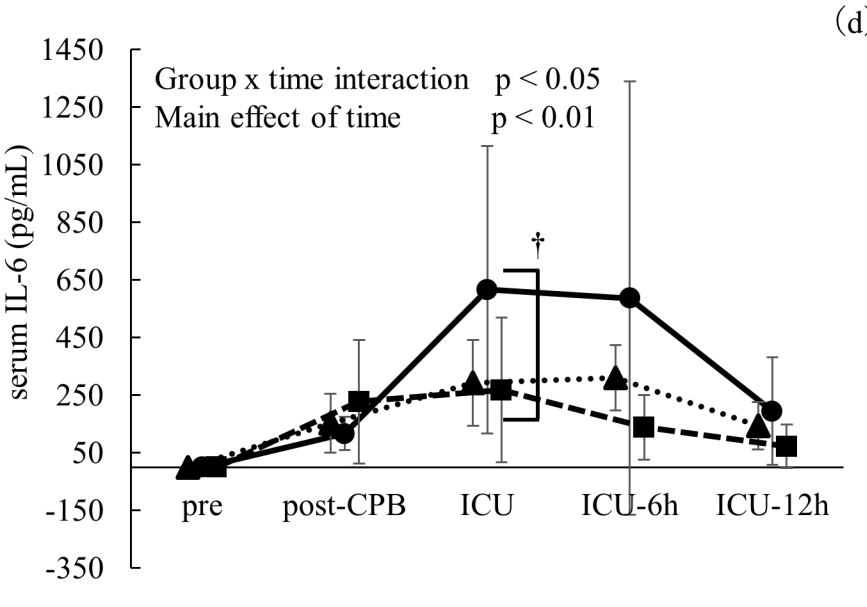
(a)



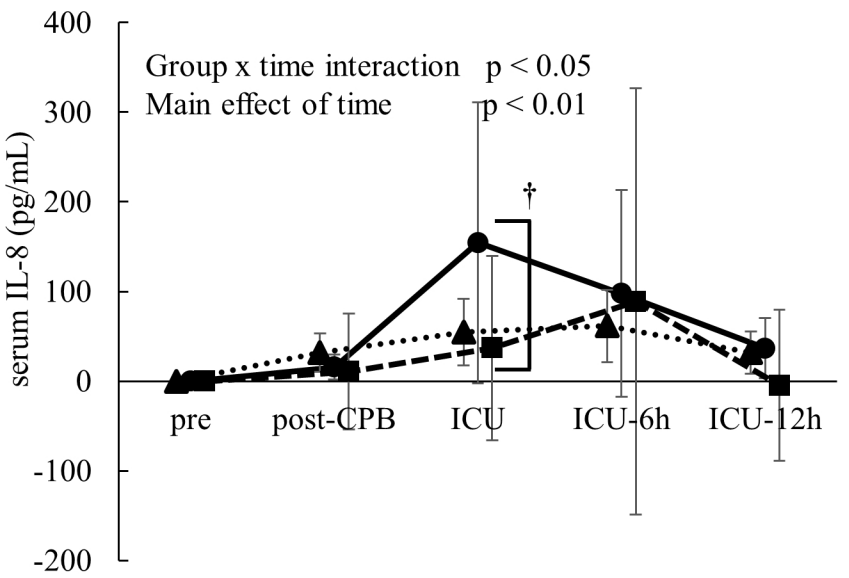
(b)



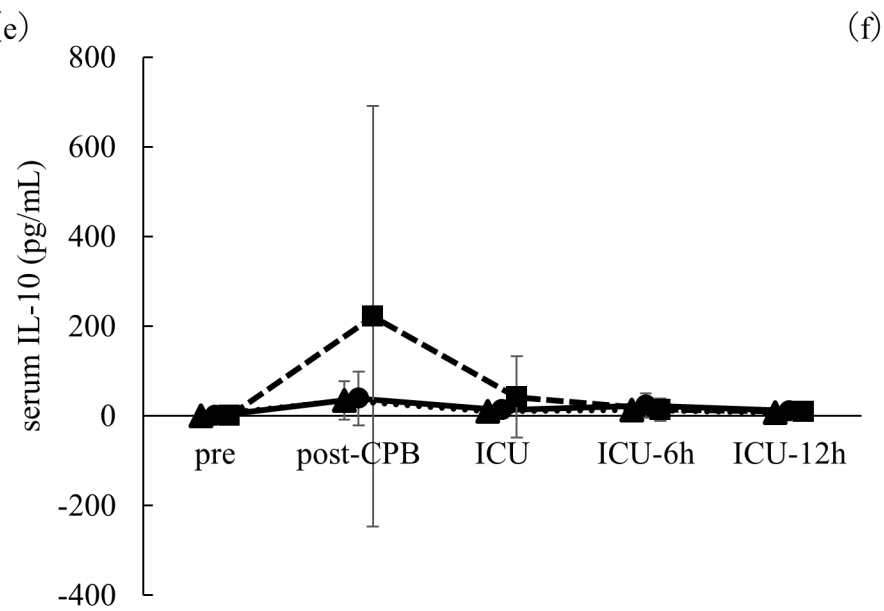
(c)



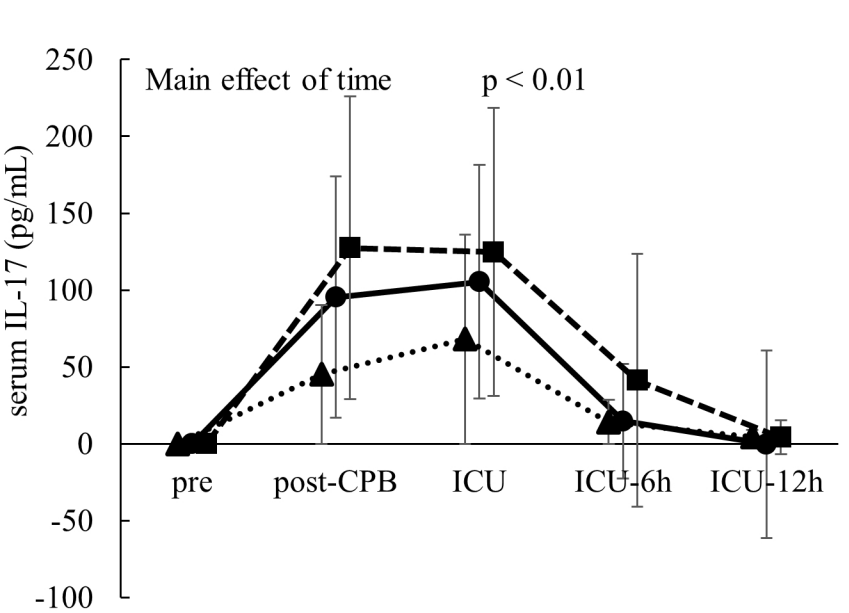
(d)



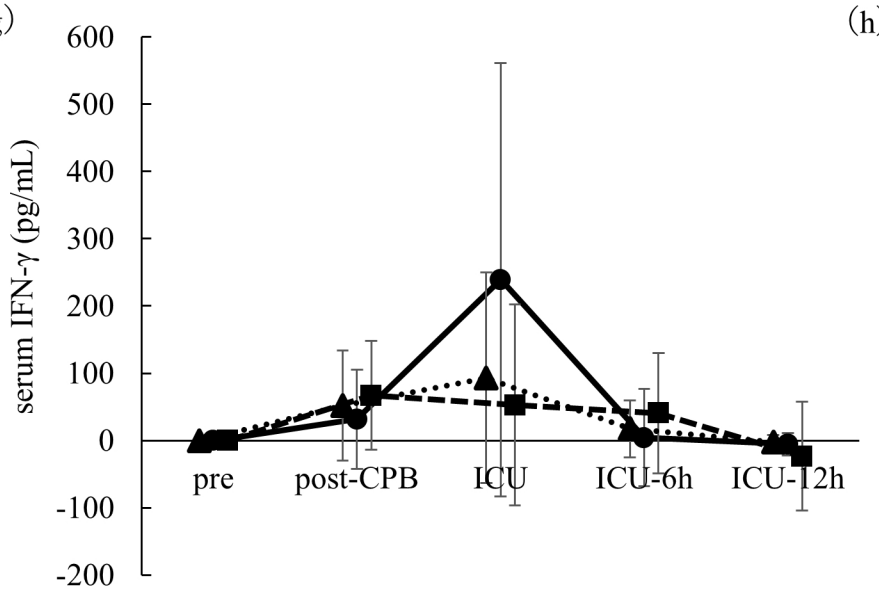
(e)



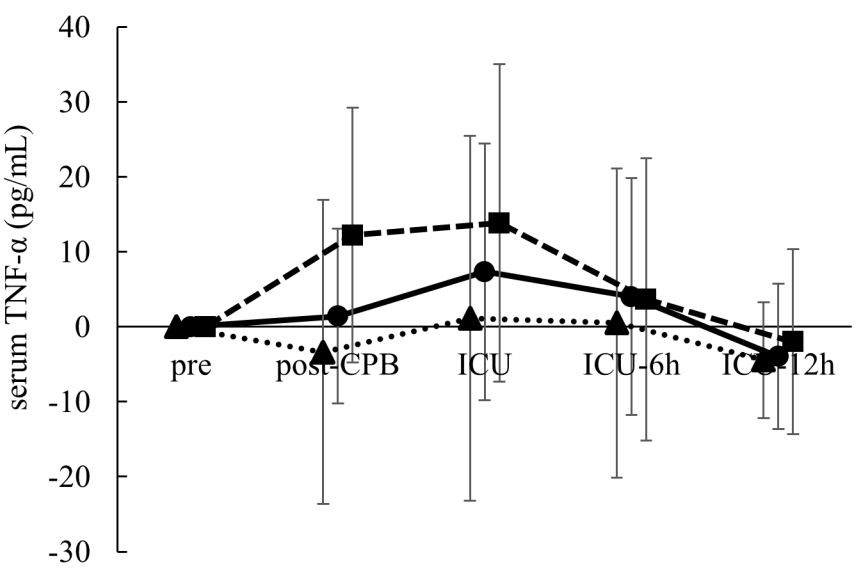
(f)



(g)



(h)



PS PMMA NHD