J Anesth (2010) 24:709–715
DOI 10.1007/s00540-010-0986-2

ORIGINAL ARTICLE

Early recovery in hemodynamics after direct hemoperfusion with polymyxin B-immobilized fibers may predict mortality rate in patients with septic shock

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Received: 31 March 2010 / Accepted: 21 June 2010 / Published online: 17 July 2010

Abstract
Purpose This retrospective and observational study attempted to determine whether the rapid improvement in hemodynamic parameters and the subsequent discontinuation or decrease of catecholamine infusion shortly after direct hemoperfusion with polymyxin B-immobilized fibers (PMX) may be strong predictors of mortality in patients with septic shock.
Methods Retrospectively, 46 patients were divided into two groups; those who survived more than 30 days after PMX (survival group, S group) and those who died within 30 days (nonsurvival group, NS group). Sequential Organ Failure Assessment (SOFA) scores, mean arterial pressure, catecholamine index (CAI), and vasopressor dependency index (VDI) were examined before and after PMX. The same parameters were examined on days 3, 4, 5, 6, 8, and 16 after PMX.
Results CAI in the S group significantly decreased from 14.7 (95% CI, 10.3–19.1) at baseline to 6.4 (95% CI, 3.7–9.2; $P < 0.001$) at post-PMX, whereas a significant decrease in CAI was not observed in the NS group (23.1; 95% CI, 15.4–30.7 to 18.1; 95% CI, 11.6–24.7; $P = 0.114$). The significant decrease in VDI at post-PMX was observed both in the S group and in the NS group. If the cutoff point of VDI at post-PMX is 0.2, there is a significant difference in numbers of the S group (VDI ≥ 0.2, $n = 24$; VDI < 0.2, $n = 2$) and NS group (VDI ≥ 0.2, $n = 8$; VDI < 0.2, $n = 20$) using Fisher's exact test.
Conclusions We concluded that the early improvement in CAI and VDI shortly after PMX might be prognostic indicators for survival.

Keywords PMX · CAI · MAP · SOFA score · Septic shock

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Introduction

Direct hemoperfusion with polymyxin B-immobilized fibers (PMX) has been widely used to treat patients with septic shock since it was licensed for clinical use in Japan in 1994. The primary mechanism of PMX was supposed to be the adsorption of endotoxin. However, recent studies show that PMX could adsorb not only endotoxin but also endogenous substances in the circulation [1, 2], which might induce hypotension at the early stage of septic shock. The precise mechanism involved in the improvement of clinical outcome with PMX has not yet been clarified. We performed two sessions of PMX for 46 of the 50 patients with septic shock who required the treatment in our hospital. Some patients showed a dramatic improvement during PMX whereas some showed less improvement. Variance of the effects of PMX might result in the clinical outcome. Therefore, we examined the clinical profiles of 46 patients with septic shock to analyze the improvement in hemodynamic parameters and the reduction in catecholamine dose shortly after PMX as predictive determinants for the clinical outcome. We used catecholamine

index score (CAI) and vasopressor dependency index (VDI) to examine hemodynamic impairment, which Cruz et al. [3] used as a dose–response relationship between vasopressor dose and mean arterial pressure (MAP) as another surrogate for the degree of hemodynamic impairment. We also examined the Sequential Organ Failure Assessment (SOFA) score, which can help to assess organ dysfunction or failure over time and is useful to evaluate morbidity. Although the scoring system was developed to describe and quantify organ function and not to predict outcome, the obvious relationship between organ dysfunction and mortality has been demonstrated in several studies [4, 5].

Subjects and methods

Fifty patients who underwent PMX with a clinical diagnosis of septic shock during the period of September 1999 to March 2007 in Saiseikai Suita Hospital were enrolled in this retrospective and observational study. Four patients, who died within 24 h and failed to undergo two sessions of PMX, were excluded. Consequently, the study consists of 46 patients who underwent two sessions of PMX during that period in our hospital. No other patients were excluded for any reason. The study received approval from the Institutional Review Board in our hospital. All patients were followed up for 30 days or until their death. An APACHE II (Acute Physiology And Chronic Health Evaluation) score was calculated at the start of PMX. The primary source of infection, causative pathogen, and adequacy of antimicrobial therapy were ascertained by specialists in microbiology. The 46 patients were divided into two groups: those who survived more than 30 days (survival group, S group) and those who died within 30 days (nonsurvival group, NS group) after PMX. Administration of catecholamine was started to keep systolic pressure more than 80 mmHg in spite of adequate fluid resuscitation, which keeps central venous pressure within normal range. PMX was performed through a double-lumen catheter placed in the femoral vein at a blood flow rate of 80 ml/min using nafamostat mesilate (Torii, Tokyo, Japan), 30–40 mg/h, as an anticoagulant. Details of the PMX procedure have been reported elsewhere [6]. All 46 patients received two sessions of PMX for 2 h. The second session of PMX started within 24 h after the first session. Consequently, day 3 means approximately 24 h after the second session of PMX.

Each patient's condition was scored with APACHE II at the start of PMX. Clinical data were recorded at baseline before the initiation of PMX (expressed as pre-PMX) and after the completion of PMX (expressed as post-PMX), on days 3, 4, 5, 6, 8, and 16. Severity of organ dysfunction or failure was expressed by using the SOFA score (range 0–24; lower scores indicate better organ function) at each time. The dose of vasoactive/vasopressor agents is expressed as CAI [7], a dimensionless valuable calculated as (dopamine dose $\times$ 1) + (dobutamine dose $\times$ 1) + (adrenaline dose $\times$ 10) + (noradrenaline $\times$ 100) + (phenylephrine dose $\times$ 100). All doses are expressed as μg/kg/min. VDI is calculated as the ratio of CAI to MAP; the higher the score, the greater the vasopressor requirement [3]. The dose of catecholamine is decided by the catecholamine infusion protocol.

Catecholamine infusion protocol

When the patient's systolic arterial pressure (SAP) decreases below 80 mmHg in spite of adequate fluid resuscitation, dopamine (DOA) infusion can be started. A dose of DOA infusion can be increased up to 15 μg/kg/min. Noradrenaline (NA) infusion can be started under two conditions: when the patient's SAP is <80 mmHg in spite of DOA infusion, and when the patient shows tachycardia (HR $\geq$ 120/min). Adrenaline (Ad) infusion, DOA infusion, and DOB infusion can be started when the patient develops bradycardia (HR $\leq$ 60) or cardiac dysfunction, which is determined by echocardiography.

When the patient's SAP increases above 80 mmHg and the other conditions are ameliorated, the dosage of Ad infusion and NA infusion can be decreased first and the dosage of DOA infusion and DOB infusion can be decreased later if the patient's HR is within the normal range.

Statistics

Data are expressed as mean (95% CI). Statistical analyses were performed using the Wilcoxon rank-sum test for the background factors, Wilcoxon signed-rank test for comparison within a group, and Wilcoxon rank-sum test for comparison between groups. Fisher's exact test was used to determine the changes. A P value <0.05 was considered significant.

Results

Severity of symptoms and background factors

The demographic data and clinical parameters before PMX are shown in Table 1. Of all patients diagnosed as having septic shock, 26 patients (M:F ratio, 17:9) were in the S group and 20 patients (M:F ratio, 16:4) were in the NS group, respectively. Age, causative pathogen, source of

Table 1 Baseline characteristics of the treatment groups

Characteristics	Mean (95% confidence interval)		
	Survival (S) group ($n = 26$)	Nonsurvival (NS) group ($n = 20$)	P value
Age, years	64 (60–68)	67 (61–73)	0.2394
Male sex, number (%)	17 (65.4)	16 (80)	0.3361
APACHE II	21 (19–23)	27 (24–30)	0.0005
Sequential Organ Failure Assessment (SOFA) score	10 (8–11)	12 (11–13)	0.0150
Mean arterial pressure, mmHg	57 (54–61)	53 (46–56)	0.2676
Catecholamine index (CAI)	14.7 (10.3–19.1)	23.1 (15.4–30.7)	0.0055
Vasopressor dependency index, $mmHg^{-1}$	0.27 (0.18–0.37)	0.48 (0.31–0.65)	0.0525
White blood cell count, 1000/μl	15.7 (10.8–20.6)	12.9 (5.7–20.0)	0.0211
PaO_2/F_IO_2	281 (236–326)	251 (180–323)	0.2631
Creatinine, mg/l	1.8 (1.2–2.4)	2.8 (1.8–3.7)	0.0047
Renal replacement therapy, number (%)	5 (19)	8 (40)	0.0187
Indication for emergency operation, number (%)	9 (35)	8 (40)	0.9999

infection, and indication for emergency surgery are very similar in both groups. The APACHE II score and the SOFA score in the NS group were significantly higher than those in the S group. The causative pathogens of sepsis are shown in Table 2.

Hemodynamic parameters before and after PMX

The physiological endpoints at baseline and at post-PMX are shown in Table 3. Regardless of the type of causative pathogens, PMX was effective for increasing MAP in all patients. MAP significantly increased from 57 mmHg at baseline to 92 mmHg ($P < 0.001$) at post-PMX in the S group, whereas CAI significantly decreased from 14.7 at baseline to 6.4 ($P < 0.001$) at post-PMX (Table 3). Although MAP increased after PMX in both groups ($P < 0.0001$), CAI significantly decreased in the S group ($P < 0.001$) only, and it did not show a significant change in the NS group. VDI decreased after PMX in both groups ($P < 0.0001$ in the S group, and $P = 0.026$ in the NS group). Based on a receiver operating characteristic (ROC) curve, among the other values that may show improvement of circulation including MAP and CAI, VDI at post-PMX can predict a significant difference between the S group and the NS group. The optimum cutoff point of VDI was 0.2. If the cutoff point of VDI at post-PMX is 0.2, there is a significant difference in numbers of the S group (VDI $\geq$ 0.2, $n = 24$; VDI < 0.2, $n = 2$) and NS group (VDI ≥ 0.2 $n = 8$; VDI < 0.2, $n = 20$) using Fisher's exact test.

Changes in the SOFA score

The SOFA score was higher in the NS group than in the S group at baseline (at pre-PMX) and at all times during the study (Fig. 1). The SOFA score in the S group decreased significantly on day 5 as compared to the baseline, whereas it increased on day 3 in the NS group (Fig. 1). The cardiovascular SOFA score was similar at baseline in both groups, but decreased at post-PMX in the S group as

Table 2 Isolated microorganisms by treatment group

	S group	NS group
Site of infection		
Intraabdominal infection	12	10
Pneumonia	4	0
Urinary tract infection	2	4
Mediastinitis	4	0
Others	4	6
Organisms		
Streptococcus pneumoniae	3	1
Methicillin-resistant *Staphylococcus aureus* (MRSA)	2	3
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	0	2
Central nervous system (CNS)	1	0
Enterococcus faecium	1	0
Klebsiella pneumoniae	2	1
Bacteroides fragilis	2	1
Escherichia coli	1	2
Enterobacter cloacae	1	2
Acinetobacter baumannii	1	0
Haemophilus influenzae	1	0
Aeromonas hydrophila	1	0
Serratia marcescens	1	0
Pseudomonas aeruginosa	0	2
Citrobacter freundii	0	1
Unknown	10	5

Table 3 Physiological endpoints by treatment group at baseline and at post-polymyxin B-immobilized fiber (PMX) hemoperfusion

Physiological endpoints	Mean (95% confidence interval)					
	S group ($n = 26$)			NS group ($n = 20$)		
	Baseline ($n = 26$)	Post-PMX ($n = 26$)	P value	Baseline ($n = 20$)	Post-PMX ($n = 20$)	P value
Mean arterial pressure, mmHg	57 (54–61)	92 (85–98)	<0.0001	53 (48–58)	71 (62–80)	<0.0001
Catecholamine index (CAI)	14.7 (10.3–19.1)	6.4 (3.7–9.1)	<0.0001	23.1 (15.4–30.7)	18.1 (11.6–24.7)	0.114
Vasopressor dependency index	0.27 (0.18–0.37)	0.08 (0.04–0.11)	<0.0001	0.48 (0.31–0.65)	0.32 (0.18–0.46)	0.026
PaO_2/F_IO_2	281 (236–326)	305 (257–353)	0.378	251 (180–323)	224 (176–271)	0.701
Creatinine, mg/dl	1.8 (1.2–2.4)	1.9 (1.3–2.6)	0.557	2.8 (1.9–3.7)	2.8 (1.9–3.7)	0.797
Renal replacement therapy	5 (19.2%)	4 (15.4%)	>0.99	8 (40%)	9 (45%)	0.9999

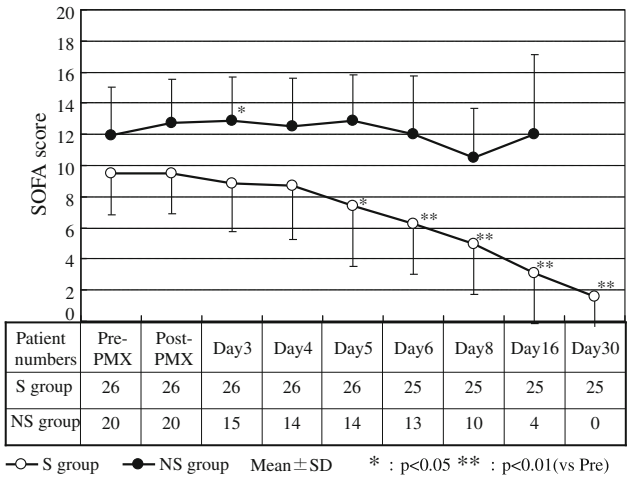

Fig. 1 Change in Sequential Organ Failure Assessment (*SOFA*) score. *Error bars* represent mean ± SD. Decrease in SOFA score indicates improvement in organ function. *PMX* polymyxin B-immobilized fiber hemoperfusion, *S group* survival group, *NS group* nonsurvival group, *Pre* pre-PMX. *Significant difference in change from baseline; $^{**}P < 0.05$

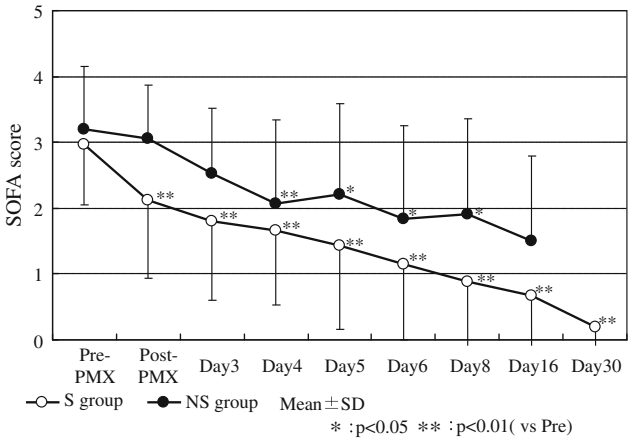

Fig. 2 Change in cardiovascular SOFA score

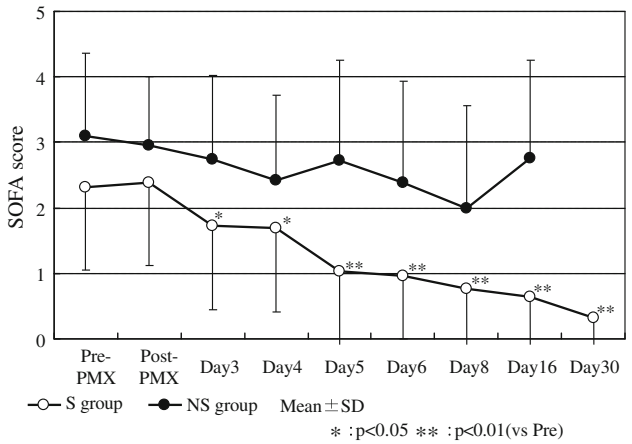

Fig. 3 Change in central nervous system (*CNS*) SOFA score

compared to the baseline, whereas it did not decrease at post-PMX in the NS group as compared to the baseline (Fig. 2). The central nervous system (CNS) SOFA score in the S group decreased on day 3 as compared to the baseline, while it did not improve in the NS group (Fig. 3). The respiratory (pulmonary) SOFA score in the S group decreased on day 8 as compared to the baseline, although it did not improve in the NS group (Fig. 4). The hepatic SOFA score did not change until day 16 as compared to the baseline and decreased later on day 30 in the S group, whereas it increased on day 3 in the NS group (Fig. 5). The renal SOFA scores of both groups did not change significantly as compared to the baseline during the study (Fig. 6). The blood coagulation system SOFA scores of both groups increased once during the early stage but decreased later on day 16 in the S group as compared to the baseline (Fig. 7).

Adverse events

During the study, all adverse events in PMX were recorded. Cartridge clotting was registered in two cases. Those two cases could be attributed to an increase in dose of

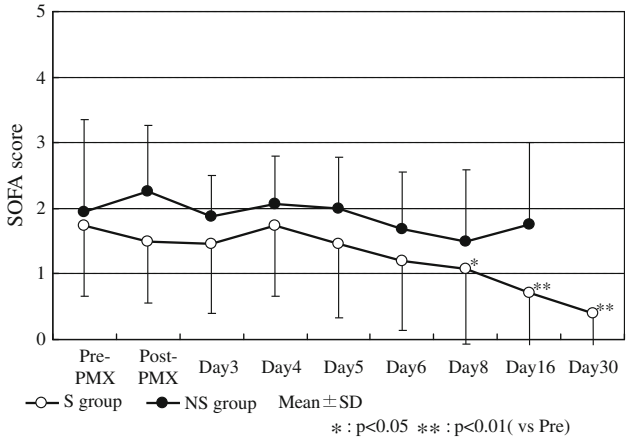

Fig. 4 Change in pulmonary SOFA score

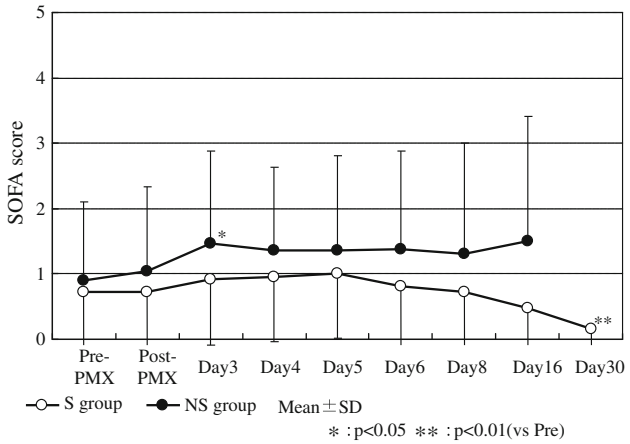

Fig. 5 Change in hepatic SOFA score

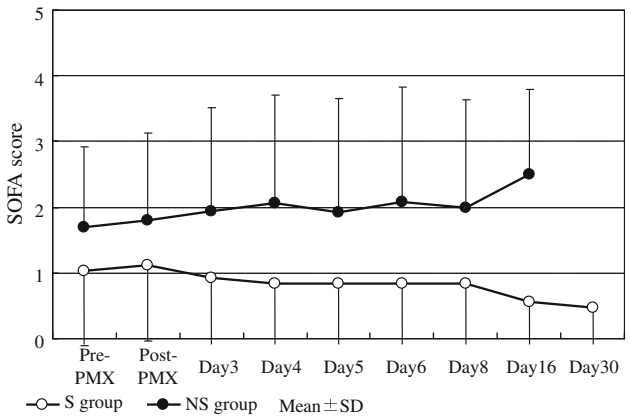

Fig. 6 Change in renal SOFA score

nafamostat mesilate from 30 to 40 mg/kg. No adverse events from hypotension and tachycardia caused by PMX per se were recorded. No adverse events indicative of

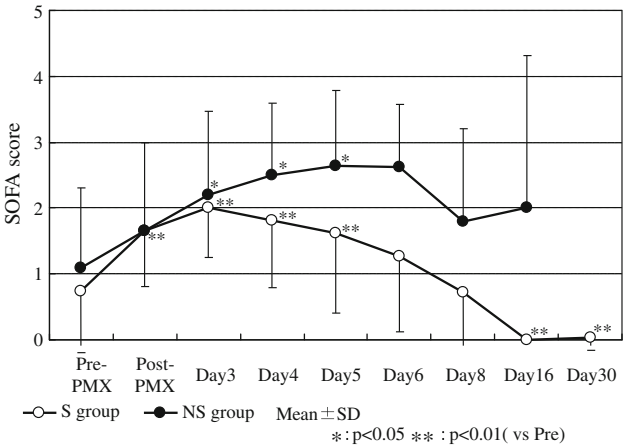

Fig. 7 Change in the blood coagulation system SOFA score

nephrotoxicity or neurotoxicity related to PMX were recorded.

Discussion

The recent randomized controlled trials (RCTs) showed PMX appeared to have a favorable effect on septic shock and was associated with better patient survival [3, 8]. Both RCTs were small and preliminary. The most recent one only targeted the patients with septic shock who underwent surgery for intraabdominal infection [3]. At present, there has been little information as to which condition indicates we should start PMX and how it would affect the prognosis of patients with septic shock. The dosage of NA infusion might be an important prognostic indicator of the severity in septic shock, because persistent vasodilation is a major hemodynamic determinant of patients who die of septic shock [9]. Several studies may have shown that MAP remains an important prognostic indicator in septic shock [10, 11].

We used CAI and VDI to examine hemodynamic impairment, which Cruz et al. [3] used as a dose–response relationship between vasopressor dose and MAP as another surrogate for the degree of hemodynamic impairment. Although MAP increased during and soon after PMX in both groups, the significant reduction in CAI was only observed in the S group but not in the NS group. A dramatic decrease was observed in the VDI at post-PMX in the S group, while a decrease in the VDI was also observed in the NS group. If the cutoff point of VDI at post PMX is 0.2, there is a significant difference in numbers of the S group and NS group, based on a ROC curve. These results might suggest that MAP in the NS group was catecholamine dependent and resulted in the poor clinical outcome. Therefore, our result suggests that the rapid reduction in

CAI and VDI at post-PMX might be important prognostic indicators in patients with septic shock.

In terms of SOFA score, a marker of improvement, showed a significant decrease on day 8 as compared to pre-PMX in the S group, whereas no decrease was observed at the early stage in the NS group. The cardiovascular SOFA score at post-PMX was found to be the most rapid responder among the other SOFA scores during the period. The rapid improvement in hemodynamic parameters and the resultant dose reduction of catecholamine might contribute to the subsequent improvement of multiple organ failure as indicated by the SOFA score in the S group. The better SOFA score at the early stage eventually resulted in the survival of the S group and the mortality of the NS group after 30 days after PMX. Therefore, we concluded that the early effectiveness of PMX observed in CAI could be an important prognostic indicator for the patient's survival.

Our study also showed PMX ameliorated septic shock regardless of the type of causative pathogen. The incidence of gram-negative bacterial infection or gram-positive bacterial infection was similar in both groups. Septic shock results from a variety of infections, including those caused by gram-negative or gram-positive bacteria and fungi. PMX was originally developed for selective adsorption of endotoxin in patients with gram-negative bacterial infection. However, Uriu et al. showed that although the severity of hyperdynamic circulation may predict the effects of PMX in patients with gram-negative septic shock, the elevation of MAP after PMX therapy in patients with septic shock was not accompanied with a decrease in blood endotoxin concentration [11]. They speculated that PMX could adsorb, in addition to endotoxin, vasoactive substances such as nitric oxide or cannabinoid that might be responsible for a decline in systemic vascular resistance in septic shock. A previous report showed that the severity of septic shock as reflected by mortality did not depend on the type of causative pathogen [12]. The other studies reported that PMX was also effective for gram-positive bacterial infection [13, 14]. It is suggested that the mechanism of PMX treatment is not endotoxin removal per se. The effect of PMX on sepsis is thought to be attributed to not only removal or reduction of endotoxin but also inhibition or elimination of the mediators of septic shock, such as cytokines, adhesion molecules, anandamide, and high mobility group 1 protein [15].

However, there are limitations to our study. First, the numbers of our patients are quite small. In addition, the cause of septic shock is multifactorial and the severities indicated in the APACHE II score at baseline were worse in the NS group. We might not have examined the effectiveness of PMX but simply observed the consequence of the severity of the illness. In spite of this limitation, the significant reduction of CAI after PMX might be a predictor for the patient's survival on day 2 shortly after PMX. The prognosis of septic patients after PMX is unpredictable. An APACHE II score, a well-known predictor that shows a patient's prognosis upon admission to the intensive care unit (ICU), has a limitation, as only the status of the patient at that point is reflected by the score; any change or difference before and after PMX cannot be reflected. Second, we are unable to comment on parameters such as cardiac index and SVR because none of our patients had invasive hemodynamic monitoring. Third, we performed two sessions, rather than one session, of PMX. Although we are unable to provide definitive answers on the duration and number of PMX required, the use of two sessions is likely to be effective from our own experience and is consistent with the large numbers of experiences in Japan.

In conclusion, our study suggests that the early improvement in the reduction of CAI and VDI shortly after PMX might be strong prognostic indicators for survival. Larger multicenter studies are required to confirm what patient condition and what timing are appropriate to require PMX.

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