Continuous Hemodiafiltration with PMMA Hemofilter in the Treatment of Patients with Septic Shock

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Septic shock is the most severe form of sepsis. It is widely accepted that cytokines play pivotal roles in the pathophysiology of septic shock. We reported previously that continuous hemodiafiltration (CHDF) using a polymethylmethacrylate (PMMA) membrane hemofilter removed various cytokines from blood continuously and efficiently, mainly by adsorption to membrane matrix of the hemofilter. Furthermore, in April 2000, we introduced to clinical practice a rapid assay system that determines blood levels of IL (interleukin)-6 in approximately 30 min. This enabled us to routinely measure blood IL-6 as an index of cytokine cascade activation in critically ill patients for real-time clinical monitoring of hypercytokinemia. The aim of the present cohort study was to evaluate the clinical efficacy of PMMA-CHDF in septic shock, a typical condition associated with hypercytokinemia. Forty-three patients with septic shock were assessed by monitoring of blood IL-6 level with a rapid assay system and immediate initiation of critical care including PMMA-CHDF for cytokine removal. Following initiation of PMMA-CHDF, early improvement of hemodynamics was noted, as well as an increase in urine output. PMMA-CHDF treatment improved both hypercytokinemia (assessed by measurement of blood IL-6 level) and dysoxia (assessed by measurement of blood lactate level). The present findings suggest that cytokine-oriented critical care using PMMA-CHDF might be an effective strategy for the treatment of septic shock.
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INTRODUCTION

Understanding of the complex pathophysiology of severe sepsis and septic shock—including initial pathogen recognition by the innate immune system and subsequent activation of cytokine cascades as well as its neurological and endocrine control, has improved greatly in recent years (1–3). As a consequence, it is widely accepted today that cytokines play pivotal roles in the pathophysiology of severe sepsis and septic shock (1–3). Although many cytokine-targeting treatment modalities for these critical conditions, including immunotherapy using monoclonal antibodies to cytokines, have been devised and clinically tested in the past two decades, few have exhibited satisfactory therapeutic effects (4).

Blood purification, originally developed for the treatment of renal failure, has subsequently been applied to critical care, aided by recent advances in related biomedical technologies as well as development of operating procedures (5–8). In particular, attempts to apply various blood purification techniques to treatment of critical illnesses, such as severe sepsis and septic shock in which humoral mediators play important roles, by removing excess humoral mediators have been documented (8–13). While the cytokine-removing effects of blood purification therapies are still controversial, the clinical efficacy of high-volume hemofiltration (HVHF), a blood purification technique with improved cytokine-removing capacity due to enhanced convection effect, has been reported in the treatment of septic shock (9,11,12).

We reported previously that continuous hemodiafiltration (CHDF) using a polymethylmethacrylate (PMMA) membrane hemofilter removed cytokines from blood continuously and efficiently, mainly by adsorption to membrane matrix of the hemofilter (6,10,13,14). We have also demonstrated that PMMA-CHDF might have a potential effect in the treatment of hypercytokinemia-related conditions such as septic multiple organ failure (15), acute respiratory distress syndrome (ARDS) (10), and severe acute

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pancreatitis (16). Furthermore, in April 2000, we introduced to clinical practice a rapid assay system that determines blood levels of IL (interleukin)-6 in approximately 30 min by chemiluminescent enzyme immunoassay (CLEIA). This enabled us to measure blood IL-6 routinely as an index of cytokine cascade activation in critically ill patients for real-time clinical monitoring of hypercytokinemia (17). We have since utilized blood IL-6 not only as a criterion for initiation and weaning of PMMA-CHDF for cytokine modulation, but also an index of therapeutic efficacy of this treatment modality. The aim of the present study was to assess the clinical efficacy of cytokine removal by PMMA-CHDF in septic shock, a typical condition associated with hypercytokinemia encountered in critical care.

MATERIALS AND METHODS

Patients

Between April 2000 and May 2007, a total of 3,264 patients were admitted to an eight-bed medical/surgical ICU of Chiba University Hospital, and 228 severe sepsis/septic shock patients were treated during ICU stay. The subjects of the present study consisted of 43 consecutive patients with septic shock who fulfilled the following criteria: (a) *De novo* septic shock; (b) PMMA-CHDF was initiated within 24 h after development of septic shock; (c) patients exhibited septic shock at ICU admission or developed it within 24 h from ICU admission. Septic shock was defined according to The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus criteria established in 1992 (18). The exclusion criteria for the present study were: (a) recurrent septic shock; (b) septic shock developed after 24 h from ICU admission; (c) an age of 18 years or younger; (d) severe heart failure (New York Heart Association: NYHA class IV).

Hemodynamic Monitoring and Initial Management of Circulatory Failure

An arterial line for continuous monitoring and trend recording of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) was placed in the radial or femoral artery. A pulmonary artery (PA) catheter (Swan-Ganz CCOmbo Pulmonary Artery Catheter, Edwards Lifesciences, Irvine, CA, USA) was placed when the physician in charge considered it necessary for circulatory management, while a central venous catheter was placed in all patients with or without a PA catheter. During PA catheterization, cardiac index (CI) and mixed venous oxygen saturation (SvO_2) were monitored with a continuous hemodynamic monitoring device (Vigilance, Edwards Lifesciences, Irvine, CA, USA). Systemic vascular resistance index (SVRI) was calculated using the following equation:

$$SVRI = 79.92 \times (MAP - \text{mean right atrium pressure})/CO/BSA.$$

Initial management of circulatory failure begun by loading crystalloid and/or 5% albumin to provide adequate fluid resuscitation until the central venous pressure (CVP) increased to 8 mmHg or higher. If a MAP under 65 mmHg was noted, continuous administrations of dopamine and/or norepinephrine were initiated. Epinephrine was used in septic shock patients who were poorly responsive to dopamine and/or norepinephrine. Doses of dopamine/norepinephrine/epinephrine were controlled according to the attending physician's judgment. Continuous administration of dobutamine was further added when an SvO_2 lower than 65% or a CI lower than 2.2 $L/min/m^2$ was observed. Since 2004, an adrenocorticotrophic hormone test has been performed, and low-dose hydrocortisone therapy (hydrocortisone 200 mg/day) has been initiated when the physician in charge considers it necessary based on the test results.

Continuous Hemodiafiltration

CHDF was initiated after adequate fluid resuscitation and catecholamine support had been provided, and the time that elapsed from ICU admission to initiation of PMMA-CHDF was recorded for each patient. Vascular access was provided by placing a 12-French flexible triple-lumen catheter (blood access triple-lumen catheter, Arrow International Inc., Reading, PA, USA) in the internal jugular vein or the femoral vein. A PMMA membrane hemofilter (Hemofeel CH-1.0, Toray Medical Co. Ltd., Tokyo, Japan) was placed in the blood circuit to adsorb cytokines in the circulating blood. Nafamostat mesilate (Futhan, Torii Pharmaceutical Co. Ltd., Tokyo, Japan) was used as anticoagulant, with the dose adjusted to maintain an activated coagulation time of 150-170 s. Operating conditions for PMMA-CHDF were as follows: blood flow rate (Q_B), 80-120 mL/min; dialysate flow rate (Q_D), 500-1000 mL/h; filtration rate (Q_F), 300-500 mL/h. Operation of the hemodiafiltration system was monitored with a personal bedside console (JUN-500, Ube Medical Co. Ltd., Tokyo, Japan). A PMMA hemofilter was replaced every 24 h in principal. Once initiated, PMMA-CHDF was basically performed without intermission until recovery from circulatory failure, defined as stability of hemodynamics without catecholamine support. Even after recovery from circulatory failure, PMMA-CHDF was continued if hypercytokinemia (defined as a blood IL-6 level of 1000 pg/mL or higher) persisted. When continuous renal replacement therapy was needed for renal support, PMMA-CHDF was continued until recovery from renal failure.

Measurement

Three different severity scores were calculated on ICU admission: Acute Physiology and Chronic Health Evaluation (APACHE) II (19); Sequential Organ Failure Assessment (SOFA) score (20); and Simplified Acute Physiology Score (SAPS) II (21). The number of failing organs was recorded on ICU admission according to departmental criteria (22). Blood lactate level as an index of dysoxia, defined as altered or abnormal tissue

oxygen metabolism, was measured on ICU admission and at intervals of 6 h thereafter, with additional measurement performed as required. Urine output was measured on ICU admission and at intervals of 1 h thereafter. Blood IL-6 level was measured at intervals of 24 h with a CLEIA-based rapid measurement system (Lumipulse f, Fujirebio, Tokyo, Japan), with additional measurement performed as required. Laboratory culture tests were performed on ICU admission and twice a week thereafter.

Statistical Analysis

Values are the mean ± standard deviation. Hemodynamic parameters, urine output, catecholamine doses, blood IL-6 level, and blood lactate level (parametric data) measured after PMMA-CHDF initiation were compared statistically with the baseline value by two-tailed paired *t*-test. *P* values less than 0.05 were considered statistically significant. A computer software package (GraphPad Prism4, GraphPad Software Inc., San Diego, CA, USA) was used for all statistical analyses.

RESULTS

Table 1 summarizes characteristics of the patients included in the present study (31 males and 12 females; age, 62.5 ± 13.3 years). The APACHE II score, SAPS II score, and SOFA score on ICU admission were 29.4 ± 8.4, 71.5 ± 18.4, and 13.7 ± 3.7, respectively. The blood lactate level on ICU admission was 72.2 ± 40.4 mg/dL. The blood IL-6 level on ICU admission was 132,300 ± 243,700 pg/mL (mean ± SD). Infection occurred most frequently in the peritoneal cavity (27.9%). Blood culture was positive in 28 cases (65.1%). Adequate initial antimicrobial coverage was performed in 41 cases (95.3%). Source control was performed in 16 cases (37.2%).

Table 1. Characteristics of Patients on ICU Admission

Male : female	31:12
Age (years)	63.5 ± 13.3
Medical/surgical	20/23
APACHE[a] II	29.4 ± 8.4
SAPS[b] II	71.5 ± 18.4
SOFA[c]	13.7 ± 3.7
Number of failing organs	2.2 ± 0.9
Laboratory data on ICU admission	
pH	7.36 ± 0.12
Base excess (mmol/L)	–5.6 ± 6.8
Blood lactate level (mg/dL)	72.2 ± 40.4
Blood IL-6 level (pg/mL) mean ± SD	132,300 ± 243,700
Median (25,75% tile)	23,480 (5,283, 101,750)
Blood urea nitrogen (mg/dL)	40.6 ± 30.0
Creatinine (mg/dL)	2.3 ± 1.3
Urinary output (mL/h)	36 ± 41
CRP[d] (mg/dL)	17.5 ± 11.1
Comorbidity	
History of cancer, *n* (%)	12 (27.9)
Diabetes mellitus, *n* (%)	9 (20.9)
Liver cirrhosis, *n* (%)	5 (11.6)
Immunosuppressive drug use, *n* (%)	5 (11.6)
Main foci of infection	
Peritoneal cavity, *n* (%)	12 (27.9)
Intestine, *n* (%)	7 (16.3)
Lung, *n* (%)	7 (16.3)
Liver/gall bladder/bile duct, *n* (%)	7 (16.3)
Kidney/urinary tract, *n* (%)	5 (11.6)
Oral cavity/pharynx/neck, *n* (%)	2 (4.7)
Unknown, *n* (%)	3 (7.0)
Blood culture-positive cases, *n* (%)	28 (65.1)
Gram-negative	21
Gram-positive	12
Fungus	2
Mixed	7
Therapy to infection	
Adequate initial antimicrobial coverage, *n* (%)	41 (95.3)
Source control, *n* (%)	16 (37.2)
Surgical operation, *n* (%)	12 (27.9)
Diffuse peritonitis, *n* (%)	9 (20.9)
Emphysematous pyelonephritis, *n* (%)	2 (4.7)
Thoracic empyema, *n* (%)	1 (2.3)
Percutaneous drainage, *n* (%)	4 (9.3)
Cholangitis/cholecystitis, *n* (%)	4 (9.3)

[a]APACHE: Acute Physiology and Chronic Health Evaluation
[b]SAPS: Simplified Acute Physiology Score
[c]SOFA: Sequential Organ Failure Assessment
[d]CRP: C-reactive protein

Figure 1 shows time-dependent changes in blood pressure and heart rate measured at intervals of 1 h for 12 h after PMMA-CHDF initiation. Significant increases in SBP and DBP were observed after 1 h of PMMA-CHDF compared with values at PMMA-CHDF initiation (SBP, 95 ± 23 mmHg versus 79 ± 18 mmHg; DBP, 44 ± 8.9 mmHg versus 39 ± 8.5 mmHg) ($P < 0.0001$, both cases). In addition, a significant increase in MAP compared with the value measured 1 h previously was detected during the initial 3 h of PMMA-CHDF (baseline, 52 ± 11 mmHg; 1 h PMMA-CHDF, 61 ± 12 mmHg; 2 h PMMA-CHDF, 66 ± 12 mmHg; 3 h

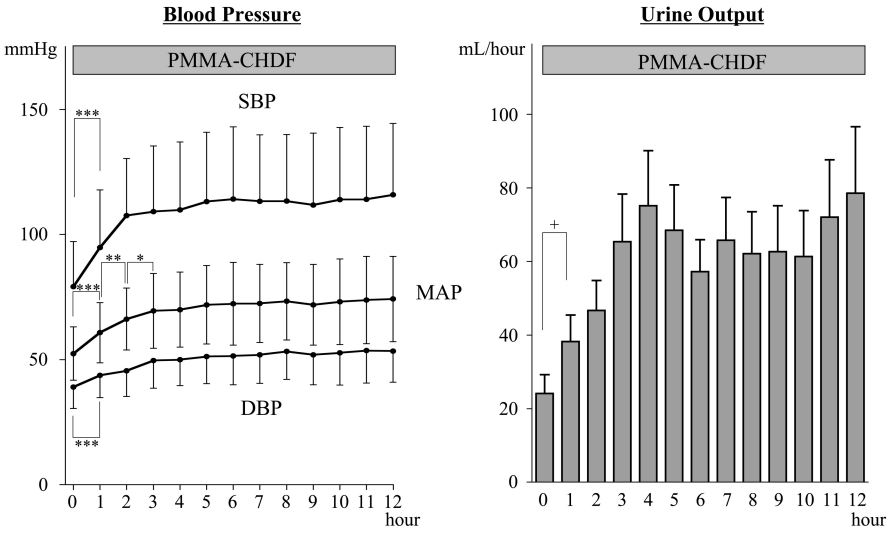

Figure 1. Changes in blood pressure and urine output after initiation of PMMA-CHDF. PMMA-CHDF: polymethylmethacrylate-continuous hemodiafiltration, SBP: systolic blood pressure, MAP: mean arterial pressure, DBP: diastolic blood pressure HR: heart rate *** $P < 0.0001$, ** $P < 0.001$, * $P < 0.05$, + $P < 0.01$.

PMMA-CHDF, 69 ± 15 mmHg) (baseline versus 1 h PMMA-CHDF, $P < 0.0001$; 1 h PMMA-CHDF versus 2 h PMMA-CHDF, $P < 0.001$; 2 h PMMA-CHDF versus 3 h PMMA-CHDF, $P < 0.05$). Urine output significantly increased after 1 h of PMMA-CDHF (baseline, 24.0 ± 33.7 mL/h; 1 h PMMA-CHDF, 38.2 ± 46.6 mL/h) ($P < 0.01$).

Figure 2 shows changes in hemodynamic parameters observed during 72 h of PMMA-CHDF treatment. MAP increased significantly after 12 h of PMMA-CDHF compared with the value at PMMA-CHDF initiation (75 ± 17 mmHg versus 52 ± 11 mmHg, $P < 0.0001$). CI gradually decreased during the 72-h PMMA-CHDF treatment, though this change was not statistically significant (3.7 ± 1.2 versus 4.3 ± 1.7, $P = 0.095$). SVRI increased significantly after 12 h of PMMA-CDHF compared with the value at PMMA-CHDF initiation (1401 ± 764 dyne/sec/cm^{-5}/m^2 versus 917 ± 352 dyne/sec/cm^{-5}/m^2, $P < 0.01$). Figure 3 shows changes in catecholamine doses during PMMA-CHDF treatment. A significant decrease in dose of dopamine/dobutamine compared with the baseline value was first noted after 12 h of PMMA-CDHF ($P < 0.05$). A significant decrease in dose of norepinephrine/epinephrine compared with the baseline value was observed after 72 h of PMMA-CDHF ($P < 0.0001$). Figure 4 shows changes in blood IL-6 level and blood lactate level observed during the 72-h PMMA-CHDF treatment. A significant decrease in blood IL-6 level compared with the baseline value was first noted after 24 h of PMMA-CDHF (20,140 ± 38,300 pg/mL versus 132,300 ± 243,720 pg/mL, $P < 0.0001$). Similarly, a significant decrease in blood lactate level compared with the baseline value was first noted after 12 h of PMMA-CDHF (47.8 ± 39.1 mg/dL versus 68.8 ± 38.7 mg/dL, $P < 0.0001$).

Table 2 summarizes findings for PMMA-CHDF and clinical outcome. The period from ICU admission to PMMA-CHDF initiation was 3.7 ± 5.2 h. Mean volume of fluid from ICU admission to CHDF initiation was 1525 ± 1182 mL. Total volume of fluid for the first 6 h was 2166 ± 776 mL. The duration of PMMA-CHDF treatment was 8.8 ± 10.2 d. Continuous administration of dopamine or norepinephrine was used in all subjects in the study when PMMA-CHDF was initiated. Recovery from circulatory failure (defined as stabilization of circulatory dynamics without catecholamine support) was achieved in 39 patients (90.7%). After recovery from circulatory failure, five cases continued PMMA-CHDF because of hypercytokinemia (defined as a blood IL-6 level of 1000 pg/mL or higher) and 12 cases continued PMMA-CHDF as renal replacement therapy. No patients in the 12 cases developed chronic renal failure. Low-dose

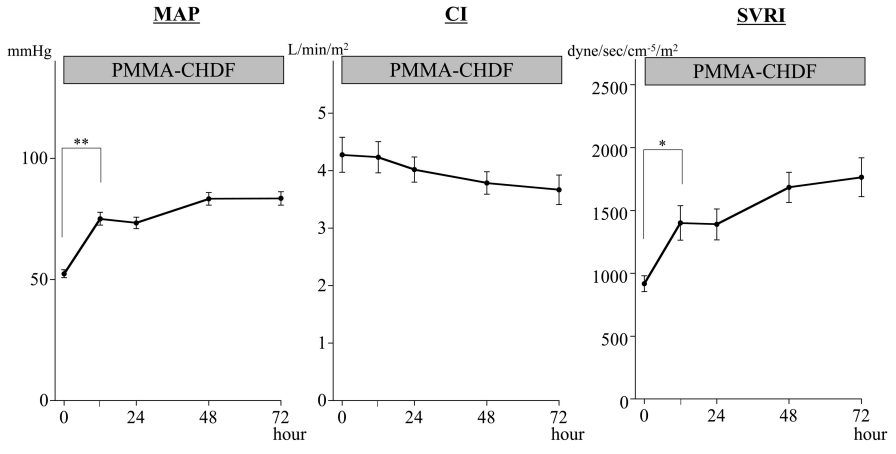

Figure 2. Changes in hemodynamic parameters during treatment with PMMA-CHDF. MAP: mean arterial pressure, CI: cardiac index, SVRI: systemic vascular resistance index ** $P < 0.0001$, * $P < 0.01$.

hydrocortisone therapy (hydrocortisone 200 mg/d) was performed in four patients. The period from ICU admission to first administration of hydrocortisone was 25.2 ± 21.1 h. The ICU survival rate, 28-day survival rate, and hospital survival rate were 81.4%, 79.1%, and 67.4%, respectively. ICU mortality was due to septic multiple organ failure (five cases), septic shock (two cases), and acute myocardial infarction (one case).

DISCUSSION

Septic shock is the most severe form of sepsis, and is characterized by a high short-term mortality between 40% and 60% (23). Although the pathophysiology, diagnosis, and treatment of severe sepsis and septic shock have been extensively investigated, the survival rate of patients with these critical conditions remains unsatisfactory. The "Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock" have been published recently to overcome this problem (24). Rivers *et al*. performed early goal-directed therapy (EGDT) in 130 patients with severe sepsis/septic shock, and reported that the EGDT provided significant benefits with respect to outcome in patients with severe sepsis/septic shock (hospital survival rate: standard therapy group versus EGDT group, 53.5% versus 69.5%, $P = 0.009$) (25). In the EGDT study, the mean base line severity scores of the EGDT treatment group (130 severe sepsis/septic shock patients) were high (APACHE II score, 21.4 ± 6.9; SAPS II score, 51.2 ± 11.1). The 28-day survival rate and hospital survival rate of the EGDT treatment group were 67.7% and 69.5%, respectively. The mean severity scores of our study subjects with septic shock on ICU admission were extremely high (APACHE II score, 29.4 ± 8.4; SAPS II score, 71.5 ± 18.4), and were higher than those of EGDT treatment group (our study subjects versus EGDT treatment group; APACHE II score, $P < 0.001$; SAPS II score, $P < 0.001$, unpaired *t*-test). The 28-day survival rate and hospital survival rate in the present study were 79.1% and 67.4%, respectively. There was no significant difference in survival rates between our study subjects and the EGDT treatment group (our study subjects versus the EGDT treatment group; 28-day survival rate, $P = 0.21$; hospital survival rate, $P = 0.68$, χ^2 test).

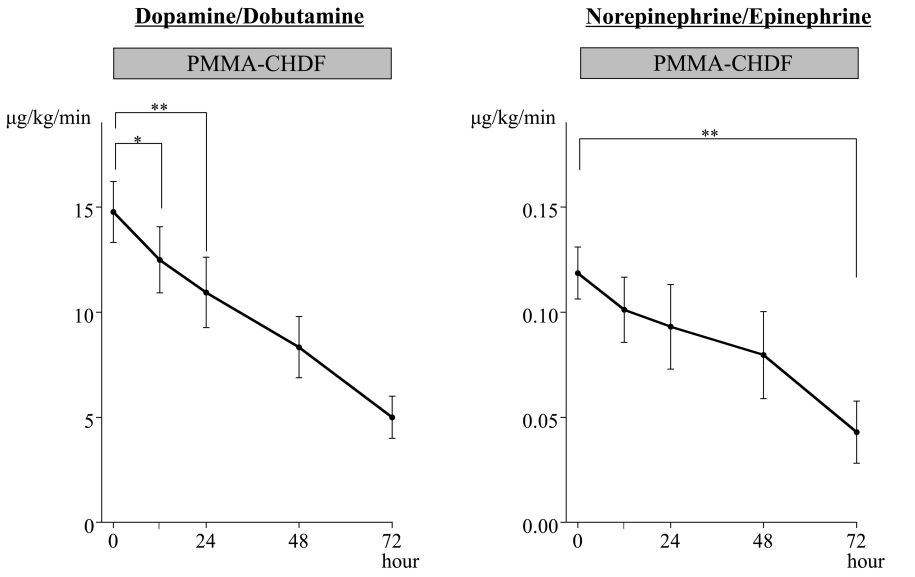

Figure 3. Changes in dosages of catecholamine during treatment with PMMA-CHDF. *$P <$ 0.05, ** $P < 0.0001$.

According to a recent and widely accepted picture of the pathophysiology of sepsis, excess pro-inflammatory cytokines play a pivotal role in the development and progression of tissue damage, shock, and organ failure (1–3). Among

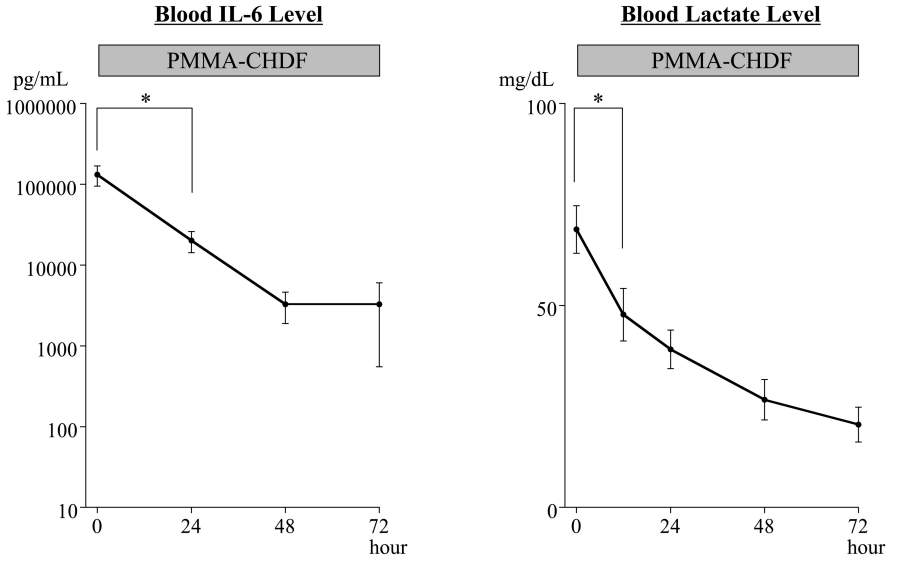

Figure 4. Changes in blood IL-6 level and blood lactate level during treatment with PMMA-CHDF. *$P < 0.0001$.

Table 2. PMMA-CHDF Data and Clinical Outcome

Duration of time from ICU admission to CHDF initiation (hours)	3.7 ± 5.2
Days on PMMA-CHDF (days)	8.8 ± 10.2
CRP after PMMA-CHDF (maximum CRP during PMMA-CHDF) (mg/dL)	8.23 ± 4.9 (23.4 ± 9.8)
Recovery from circulatory failure, *n* (%)	39 (90.7)
Duration of time from CHDF initiation to recovery from circulatory failure (hours)	84.2 ± 89.3
Length of ICU stay (days)	18.4 ± 28.8
ICU survival, *n* (%)	35 (81.4)
28-day survival, *n* (%)	34 (79.1)
Hospital survival, *n* (%)	29 (67.4)

these pro-inflammatory cytokines, IL-6 has a longer half-life in blood than TNF-α and IL-1β, and the blood level of this cytokine is reported to be a good index of cytokine cascade activation in critical illnesses such as sepsis and septic shock (26,27). In 2000, we introduced to critical care treatment a rapid assay system for determination of blood IL-6 level in approximately 30 min by automated chemiluminescent enzyme immunoassay. Using this assay system, we demonstrated a significant positive correlation between peak IL-6 blood level and maximum SOFA score in patients with systemic inflammatory response syndrome (SIRS)/sepsis/severe sepsis/septic shock, as well as an extremely high blood IL-6 level in septic shock far exceeding the level in SIRS/sepsis/severe sepsis (17). Based on these findings, we routinely use measurement of blood IL-6 level to assess the severity of critically ill ICU patients and as a criterion for initiation or weaning of PMMA-CHDF. Our aim is to establish scientific cytokine-oriented critical care, which may be most effective in patients with extremely high blood IL-6 levels, as in our study subjects with septic shock exhibiting a mean blood IL-6 level of 132,300 ± 243,700 pg/mL on ICU admission.

The mechanisms of cytokine removal by blood purification include convection, diffusion, and adsorption. The extent of cytokine removal by a particular blood purification therapy (utilizing any of these mechanisms alone or in combination with another) principally depends on the material and shape of the hemofilter/hemodialyzer/adsorber used and the operating conditions employed. Many investigations of blood purification therapy for septic shock have reported the clinical efficacy of high-volume hemofiltration (HVHF) with enhanced convection effect (9,11,12,28). Honore *et al*. (9) performed HVHF using a polysulphone membrane hemofilter for 4 h with a total filtrate volume of 35 L in 20 patients with septic shock, and reported clinical findings suggesting that initiation of HVHF early after the diagnosis of septic shock might improve hemodynamics and 28-day survival of patients. Cole *et al*. (11) performed HVHF using a polyacrylonitrile membrane hemofilter for 8 h at a filtration rate of 6 L/h in 11 patients with septic shock, and reported that it reduced the dose of norepinephrine required to maintain circulation, a clinically useful effect. Cornejo *et al*. (12) performed HVHF using a polysulphone membrane hemofilter for 10 h at a filtration rate of 100 mL/kg/h in 20 patients with septic shock, and reported a decrease in requirement of norepinephrine, an improved blood lactate level, and a high survival rate, all due to improvement of hemodynamics. Stimulated by these promising clinical results, a large-scale clinical trial to examine the therapeutic effects of HVHF in septic shock is now in progress (28).

We previously calculated the clearance of CHDF using hemofilters made of various materials such as PMMA, polyacrylonitrile, polysulphone, and ethylene vinyl alcohol as an index of ability to remove substances from blood, and examined the effects of hemofilter membrane materials on cytokine removal. We found that CHDF using a PMMA membrane hemofilter exhibited a higher capacity to remove cytokines than CHDF using a hemofilter made of a different material (10,29). This high capacity for cytokine removal of PMMA-CHDF was principally ascribable to adsorption of cytokines to the hemofilter membrane. Furthermore, blood cytokine levels in critically ill patients were significantly decreased after PMMA-CHDF treatment for 3 d (10). Based on these findings, we concluded that the PMMA membrane has a capacity to remove cytokines superior to that of any other membrane we tested, and that CHDF using a PMMA membrane removed cytokines more efficiently at higher levels of blood cytokines. We also concluded that PMMA-CHDF significantly reduced blood cytokine levels when baseline values of blood cytokine levels were high (10,13,14). PMMA-CHDF removes cytokines from blood mainly by adsorption, rather than convection, and does not require high blood flow and a large volume of sterile fluid.

The present study examined the clinical efficacy of PMMA-CHDF in patients with septic shock exhibiting extremely high blood IL-6 levels, and demonstrated a significant decrease in blood IL-6 level during PMMA-CHDF treatment for 72 h. The high capacity of PMMA-CHDF to remove cytokines thus resulted in excellent therapeutic effects. The present study also demonstrated a significant decrease in blood lactate level during PMMA-CHDF, which indicated improvement of dysoxia, a condition playing an important role in the pathophysiology of septic shock. Among hemodynamic parameters, significant increases in SBP, DBP, and MAP were observed after 1 h of PMMA-CHDF treatment. A significant increase in MAP compared with the value measured 1 h previously was noted until 3 h after initiation of PMMA-CHDF. Although no significant change in

cardiac index was noted, SVRI increased significantly 12 h after initiation of PMMA-CHDF compared with the baseline value. Although the mechanism by which improvement of hemodynamics occurs as early as 1 h after PMMA-CHDF initiation remains to be determined in detail, it might involve removal by PMMA-CHDF of a vasodilating mediator (or mediators).

The present study had some limitations. First, the design of the present study was a prospective cohort study with no control groups. Second, the size of sample was small. Third, this study was performed over a long period of time. Fourth, this study was performed in a single center. A randomized, controlled trial with a larger sample size is needed to confirm the clinical efficacy of PMMA-CHDF in treating septic shock.

CONCLUSION

The clinical efficacy of PMMA-CHDF in consecutive patients with septic shock on ICU admission or who developed it early during their ICU stay was assessed by monitoring of blood IL-6 level with a rapid assay system and immediate initiation of critical care including PMMA-CHDF for cytokine removal. Following initiation of PMMA-CHDF, early improvement of hemodynamics was noted, as well as an increase in urine output. PMMA-CHDF treatment improved both hypercytokinemia (assessed by measurement of blood IL-6 level) and dysoxia (assessed by measurement of blood lactate level). Although further investigation is needed to establish the clinical usefulness of cytokine-oriented critical care involving PMMA-CHDF, the present findings suggest that it might be an effective strategy for the treatment of septic shock.

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