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• *BASIC RESEARCH* •

Influence of continuous veno-venous hemofiltration on the course of acute pancreatitis

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Abstract

AIM: To investigate whether continuous veno-venous hemofiltration (CVVH) in different filtration rate to eliminate cytokines would result in different efficiency in acute pancreatitis, whether the saturation time of filter membrane was related to different filtration rate, and whether the onset time of CVVH could influence the survival of acute pancreatitis.

METHODS: Thirty-seven patients were classified into four groups randomly. Group 1 underwent low-volume CVVH within 48 h of the onset of abdominal pain (early CVVH, n = 9). Group 2 received low-volume CVVH after 96 h of the onset of abdominal pain (late CVVH, n = 10). Group 3 underwent high-volume CVVH within 48 h of the onset of abdominal pain (early CVVH, n = 9). Group 4 received high-volume CVVH after 96 h of the onset of abdominal pain (late CVVH, n = 9). CVVH was sustained for at least 72 h. Blood was taken before hemofiltration, and ultrafiltrate was collected at the start of CVVH and every 12 h during CVVH period for the purpose of measuring the concentrations of TNF-α, IL-1β and IL-6. The concentrations of TNF-α, IL-1β and IL-6 were measured by swine-specific ELISA. The Solartron 1 255 B frequency response analyzer (British) was used to observe the resistance of filter membrane.

RESULTS: The survival rate had a significant difference (94.44% *vs* 68.42%, P<0.01) high-volume and low-volume CVVH patients. The survival rate had also a significant difference (88.89% *vs* 73.68%, P<0.05) between early and late CVVH patients. The hemodynamic deterioration (MAP, HR, CVP) was less severe in groups 4 and 1 than that in group 2, and in group 3 than in group 4. The adsorptive saturation time of filters membranes was 120-180 min if the filtration rate was 1 000-4 000 mL/h. After the first, second and third new hemofilters were changed, serum TNF-α concentrations had a negative correlation with resistance (r: -0.91, -0.89, and -0.86, respectively in group 1; -0.89, -0.85, and -0.76, respectively in group 2; -0.88, -0.92, and -0.82, respectively in group 3; -0.84, -0.87, and -0.79, respectively in group 4). The decreasing extent of TNF-α, IL-1β and IL-6 was significantly different between group 3 and group 1 (TNF-α P<0.05, IL-1β P<0.05, IL-6 P<0.01), between group 4 and group 2 (TNF-α P<0.05, IL-1β P<0.05, IL-6 P<0.01), between group 1 and group 2 (TNF-α P<0.05, IL-1β P<0.05, IL-6 P<0.05), and between group 3 and group 4 (TNF-α P<0.01, IL-1β P<0.01, IL-6 P<0.05), respectively during CVVH period. The decreasing extent of TNF-α and IL-1β was also significantly different between survival patients and dead patients (TNF-α P<0.05, IL-1β P<0.05). In survival patients, serum concentration of TNF-α and IL-1β decreased more significantly than that in dead patients.

CONCLUSION: High-volume and early CVVH improve hemodynamic deterioration and survival in acute pancreatitis patients. High-volume CVVH can eliminate cytokines more efficiently than low-volume CVVH. The survival rate is related to the decrease extent of TNF-α and IL-1β. The adsorptive saturation time of filter membranes are different under different filtration rate condition. The filter should be changed timely once filter membrane adsorption is saturated.

Key words: Venovenous hemofiltration; Acute pancreatitis; TNF-α; IL-1β; IL-6

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INTRODUCTION

Excessive activation of inflammatory mediator cascade during severe acute pancreatitis is a major cause of multiple organ dysfunction associated with a high mortality[1]. Non-selective elimination of pancreatitis-related mediators is a preventive measure against the systemic complications of the disease. Continuous veno-venous hemofiltration (CVVH) has been shown to have considerable benefit for the treatment of multiple organ dysfunction secondary to sepsis[2,3]. Clinical and experimental studies indicate that CVVH is able to eliminate small and medium-sized inflammatory mediators such as cytokines[4-6]. These data suggest that the mechanisms of

mediator elimination are convective filtration through the filters and adsorption of mediators to the filter membrane. Whether different filtration rate can induce different efficiency in removing inflammatory mediators is controversial[7,8]. If filter membrane adsorption reaches saturation, the filter should be changed timely. However, little is known about the saturation time of filter membrane. Whether the filtrate rate can change membrane saturation time is unclear. The present study therefore investigated whether low-volume and high-volume CVVH could eliminate cytokines in acute pancreatitis, and whether the onset time of CVVH could affect the survival of acute pancreatitis patients. By measuring electrical resistance of filter membranes with the impedance method, we studied the adsorptive saturation time of filter membranes. Furthermore, we investigated whether the saturation time of filter membrane was related to different filtration rates.

MATERIALS AND METHODS

Patients

Thirty-seven patients (21 males, 16 females, averaging 51.4±11.6 years in age with a range of 36-70 years) with acute pancreatitis were studied. Prior to the study, all patients or their relatives were informed in detail, and consent was obtained. The diagnosis was based on typical abdominal pain associated with an increase in serum amylase and lipase concentration. All the patients studied also had morphologic abnormalities compatible with acute pancreatitis demonstrated by contrast-enhanced computed tomography and/or ultrasonography. Pancreatitis was biliary origin in 31 patients, alcoholic origin in 4 patients, and unknown origin in 2 patients.

Diagnostic criteria for severe acute pancreatitis (SAP) standardized by the British Society of Gastroenterology Working Party on the management of acute pancreatitis in 1995[9] and diagnostic criteria for multiple organ dysfunction syndrome (MODS) standardized by American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) were applied[10]. The frequencies of various complications observed in patients with severe pancreatitis are reported in Table 1. All patients initially received standard conservative treatment. Two patients with severe pancreatitis underwent surgery for infection of pancreatic necrosis. Mean arterial blood pressure (MAP), central venous pressure (CVP), and heart rate (HR) were monitored continuously. The primary end point was mortality on d 14.

Table 1 Complications in 37 patients with acute pancreatitis

Complication	Patients (*n*)
Pancreatic necrosis	20
Pulmonary involvement (pleural effusion, atelectasis)	16
Pancreatic fluid collection	12
Renal failure	6
Pseudocysis	5
Infection	4
Multi-organ failure	4

Patients were classified into four groups randomly by the onset of acute pancreatitis and the intensity of CVVH.

Group 1: Nine cases underwent low-volume CVVH within 48 h of the onset of abdominal pain (early CVVH);

Group 2: Ten cases underwent low-volume CVVH after 96 h of the onset of abdominal pain (late CVVH);

Group 3: Nine cases received high-volume CVVH within 48 h of the onset of abdominal pain (early CVVH);

Group 4: Nine cases received high-volume CVVH after 96 h of the onset of abdominal pain (late CVVH).

Procedures of CVVH

A double lumen catheter was inserted into the internal jugular vein of 23 patients and into the femoral vein of 14 patients to establish vascular access. The blood flow rate ranged 250-300 mL/min. CVVH was sustained for at least 72 h. The substitution fluid was infused at a rate of 1 000 mL/h in low-CVVH group and at a rate of 4 000 mL/h in high-CVVH group[11] in a pre-diluted manner (before hemofiltration). The substitution fluid rate was equal to the ultrafiltrate rate. An AN69 hemofilter (HOSPAL. Industrie-69 330 Meyzieu, France, 1.2 m^2) was used and changed every 24 h. To prevent clotting, low molecular weight heparin (Fraxi, 0.4 mL) was given at the start of CVVH. Then Fraxi was infused into the blood circuit before filtration every four hours, and ceased when the patient displayed hemorrhagic tendencies, such as hematemesis, hemafecia and emorrhagia nasalis.

Application of frequency response analyzer

The Solartron 1 255 B frequency response analyzer (UK) was used to observe the resistance of filter membrane. Filters were holed near the inlet and outlet of dialysate. Two ends of pyrogen-free electrode (alloy of nickel chromium thread coated with pvc. diameter: 0.5 mm) of the Solartron 1 255 B frequency response analyzer were fixed to the periphery of filter membranes through the holes. Then the holes were sealed up by pyrogen-free gel bar gun. The resistance of filter membrane was constantly observed and recorded every 10 min.

Cytokine measurement

Blood was taken before hemofiltration, the ultrafiltrate was collected at the start of CVVH and every 12 h during CVVH for the purpose of measuring the concentration of TNF-α, IL-1β, and IL-6. To analyze the correlation of serum inflammatory mediators with resistance of filter membrane, blood samples for measuring TNF-α were collected every 10-min when a new filter was used until the resistance of filter membrane reached the plateau. The concentrations of TNF-α, IL-1β, and IL-6 were measured by swine-specific ELISA (Sigma, USA).

Statistical analysis

Student' s *t*-test was used to compare the data between groups. The data were expressed as mean±SD. The survival time was calculated by the Kaplan-Meier analysis and compared by the log-rank test. Hemodynamic parameters were evaluated by one-way analysis of variance (ANOVA). The change of hemodynamic parameters, cytokines, and electrical resistance of filter membrane was evaluated and by ANOVA. The correlation between serum TNF-α and the resistance of filter membrane was determined by Pearson correlation analysis. $P<0.05$ was considered statistically significant.

RESULTS

Survival

Among the 19 patients in groups 1 and 2 who underwent low-volume CVVH, 13 patients were still alive at the end of the observation period. In groups 3 and 4, among the 18 patients who underwent high-volume CVVH, 17 patients were still alive at the end of the observation period (Figure 1A). The survival rate was significantly different between the patients undergone high-volume and low-volume CVVH (94.44% *vs* 68.42%, $P<0.01$). The data showed that the survival could be improved significantly by high-volume CVVH.

In groups 1 and 3, among the 18 patients who underwent early CVVH, 16 patients were still alive at the end of the observation period. In groups 2 and 4, among the 19 patients who received late CVVH, 14 patients were still alive at the end of the observation period (Figure 1B). The survival rate was significantly different between the patients who had undergone early and late CVVH (88.89% *vs* 73.68%, $P<0.05$). The results suggested that early CVVH could improve survival of acute pancreatitis patients.

Hemodynamic parameters

Seventy-two hours after CVVH, MAP and CVP had no significant difference between group 1 and group 3 ($P>0.05$). MAP and CVP significantly decreased in group 2 compared to group 4 ($P<0.05$, Table 2). The hemodynamic diversity (MAP, HR, CVP) was different between group 2 and group 4 ($P<0.05$). The hemodynamic deterioration (MAP, HR, CVP) was less severe in group 4 than in group 2 ($P<0.05$). The data demonstrated that high-volume CVVH significantly improved hemodynamic deterioration compared to low-volume CVVH.

MAP and CVP had a significant difference in groups 2 and 4 compared to groups 1 and 3 ($P<0.01$), 72 h after CVVH (Table 2). The hemodynamic diversity (MAP, HR, CVP) was different between groups 1 and 2 ($P<0.05$) and between groups 3 and 4 ($P<0.01$). The hemodynamic deterioration (MAP, HR, CVP) was less severe in groups 1 and 3 than in groups 2 and 4 ($P<0.05$). These data showed that CVVH could improve hemodynamic parameters in pancreatitis, and that early CVVH significantly improved hemodynamic deterioration than compared to late CVVH.

Resistance of filter membrane in different filtration flow rate

The filter membrane is an insulator before it contacts with blood or substitution fluid. In our study, when pyrogen-free saline passed through the blood compartment of filter, the resistance of filter membranes did not change at different time points. Electrical resistance tended to change in all treatment groups ($P<0.05$, Table 3). The highest resistance of filter membrane demonstrated at 120 min in groups 1 and 2, and at 180 min in groups 3 and 4. It also showed that the adsorptive saturation time of filter membranes was at 120 and 180 min in 1 000 mL/h filtration rate and in 4 000 mL/h filtration rate, respectively. The resistance at the same time point was significantly different ($P<0.01$) between groups 4 and 2, and groups 3 and 1. The data demonstrated that the adsorptive saturation time of filter membranes was different under different filtration rate conditions. The adsorptive saturation time of filter membranes was 120-180 min if the filtration rate was 1 000-4 000 mL/h.

Serum TNF-α levels and relationship between TNF-α and resistance

Serum TNF-α levels decreased significantly ($P< 0.01$) until the resistance reached the plateau (120 min in group 2 and 180 min in group 4) after a new filter was exchanged (Table 4). Then, TNF-α concentrations decreased slowly in groups 1

Table 2 Clinical outcome parameters of acute pancreatitis (mean±SD)

Parameter	Group	Pre-CVVH	12 h	24 h	36 h	48 h	60 h	72 h
MAP (kPa)	1	14.00±1.60	14.13±1.87	14.13±2.00	13.33±1.87	13.07±2.00	13.07±1.60	13.20±2.13
	2	12.13±1.87	12.10±1.65	12.10±1.87	11.20±2.13	11.14±1.60	10.27±1.58	9.33±2.13[a,b]
	3	14.13±2.00	14.17±1.60	13.87±1.87	13.85±1.85	13.87±2.13	13.60±1.62	13.87±2.00
	4	12.13±1.60	12.15±1.86	12.00±1.88	12.13±1.47	11.73±2.00	11.47±1.87	10.80±1.89[a,c]
HR (beats/min)	1	105±20	106±18	102±24	93±21	90±22	91±25	88±19
	2	120±24	116±20	110±22	112±18	114±19	120±20	118±25
	3	106±22	104±21	96±24	88±19	84±21	84±18	86±20
	4	119±18	110±24	102±22	104±25	101±20	96±20	90±18
CVP (kPa)	1	0.77±0.15	0.77±0.14	0.79±0.13	0.81±0.11	0.84±0.16	0.80±0.17	0.81±0.15
	2	0.67±0.17	0.68±0.13	0.71±0.12	0.73±0.14	0.69±0.13	0.64±0.14	0.55±0.14[a,b]
	3	0.77±0.14	0.80±0.14	0.81±0.13	0.81±0.14	0.80±0.12	0.83±0.13	0.81±0.14
	4	0.69±0.12	0.64±0.11	0.67±0.14	0.67±0.14	0.69±0.13	0.64±0.10	0.60±0.14[a,c]

[a]$P<0.05$ *vs* Pre-CVVH; [b]$P<0.01$ *vs* group 1; [c]$P<0.05$ *vs* group 2.

Table 3 Resistance level of different groups of acute pancreatitis patients (mean±SD)

Group	0 min	30 min	60 min	90 min	120 min	150 min	180 min	210 min
1	0.37±0.07	0.93±0.08	1.32±0.15	1.59±0.10	1.72±0.11	1.72±0.10	1.70±0.09	1.72±0.13
2	0.37±0.09	0.94±0.07	1.35±0.08	1.60±0.07	1.72±0.10	1.72±0.13	1.71±0.14	1.72±0.10
3	0.37±0.05	1.67±0.11	2.68±0.14	3.58±0.15	4.11±0.12	4.27±0.11	4.29±0.15	4.27±0.11
4	0.37±0.07	1.66±0.09	2.70±0.11	3.57±0.15	4.09±0.14	4.28±0.15	4.29±0.16	4.28±0.15
Saline	0.37±0.05	0.38±0.09	0.35±0.08	0.36±0.12	0.37±0.11	0.36±0.13	0.36±0.15	0.36±0.13

Table 4 TNFα concentration after changing filter of acute pancreatitis (mean±SD, ng/L)

Group	Flter	0 min	30 min	60 min	90 min	120 min	150 min	180 min	210 min
2	1st	1 932±248	1 825±292	1 711±254	1 603±268	1 562±247	1 543±224	1 532±248	1 520±228
	2nd	1 449±237	1 362±215	1 295±239	1 221±281	1 208±272	1 201±268	1 197±274	1 191±272
	3rd	1 173±253	1 107±213	1 035±246	1 018±274	982±237	978±226	962±225	954±225
4	1st	1 893±248	1 786±292	1 676±254	1 592±268	1 501±247[b]	1 468±224	1 440±248	1 431±247
	2nd	1 365±237	1 280±215	1 205±239	1 136±281	1 093±272	1 082±268	1 067±274	1 060±238
	3rd	985±253	903±213	846±346	784±274	751±237	730±226	718±345	711±235

[b]$P<0.01$ *vs* group 2 1st.

and 3 compared to groups 2 and 4 ($P< 0.05$). When the first filter was used, TNF-α concentration decreased significantly in groups 4 and 3 compared to groups 2 and 1 ($P<0.05$). The data suggested that there was a correlation between resistance and serum TNF-α concentration. When the resistance increased, serum TNF-α concentration decreased significantly in the same group after a new filter was installed. After the first, second, and third new hemofilters were exchanged, serum TNF-α concentration was negatively correlated with the resistance (r: -0.91, -0.89, and -0.86 in group 1; -0.89, -0.85, and -0.76 in group 2; -0.88, -0.92, and -0.82 in group 3; -0.84, -0.87, and -0.79 in group 4). The data showed that the time point at which the resistance reached plateau was the membrane adsorptive saturation time, and the resistance could reflect the mass of inflammatory mediators for membrane adsorption.

Cytokine levels in different groups

Before CVVH, serum concentrations of TNF-α, IL-1β, and IL-6 had no significant difference between groups 3 and 1, and between groups 4 and 2 ($P>0.05$). Serum concentrations of TNF-α, IL-1β and IL-6 tended to decrease in all treatment groups during CVVH. The decreasing extent of TNF-α, IL-1β and IL-6 was different between groups 3 and 1 (TNF-α $P<0.05$, IL-1β $P<0.05$, IL-6 $P<0.01$), between groups 4 and 2 (TNF-α $P<0.05$, IL-1β $P<0.05$, IL-6 $P<0.01$), (Figure 2A-C).The data demonstrated that the diversity of TNF-α, IL-1β and IL-6 levels increased 72 h after CVVH. The results showed that high-volume CVVH could eliminate cytokines more effectively than low-volume CVVH.

The decreasing extent of TNF-α, IL-1β and IL-6 was different between groups 1 and 2 (TNF-α $P<0.05$, IL-1β $P<0.05$, IL-6 $P<0.05$), between groups 3 and 4 (TNF-α $P<0.01$, IL-1β $P<0.01$, IL-6 $P<0.05$) during CVVH (Figure 2A-C). Serum concentrations of TNF-α, IL-1β, and IL-6 decreased more significantly in groups 1 and 3

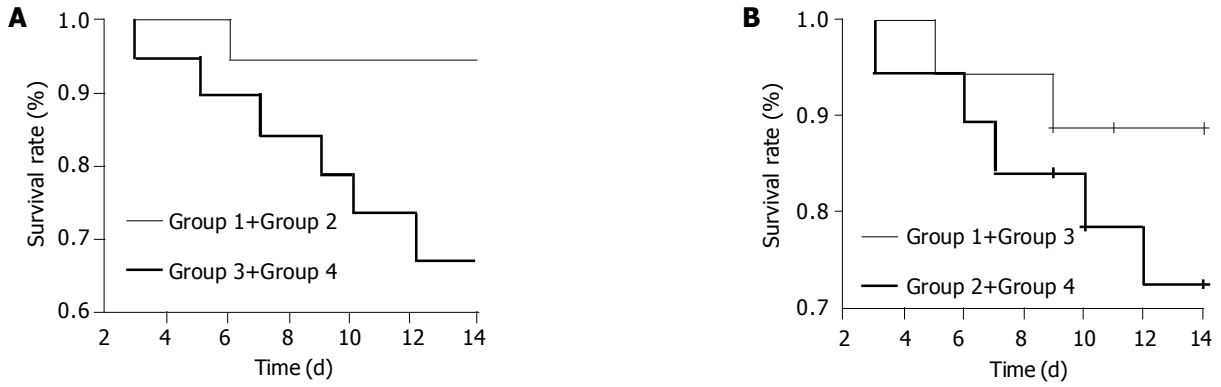

Figure 1 Survival rate of different intensifying CVVH (**A**) and different start time of CVVH (**B**).

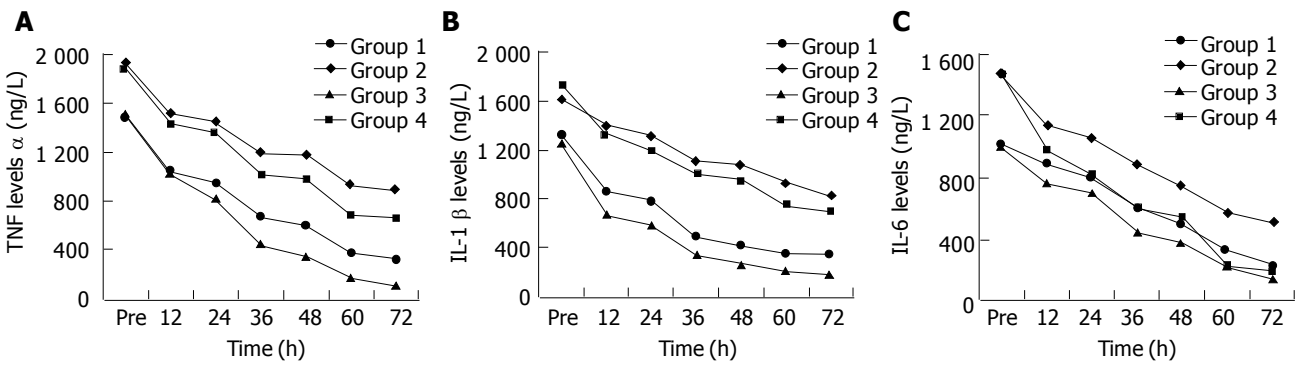

Figure 2 Serum level of TNFα (**A**), IL-1β (**B**), and IL-6 (**C**) in different groups of acute pancreatitis patients.

than in groups 2 and 4 (TNF-α $P<0.05$, IL-1β $P<0.05$, IL-6 $P<0.01$). Early CVVH decreased serum concentrations of TNF-α, IL-1β and IL-6 more efficiently than late CVVH. The data showed that early CVVH could decrease the excessive activation of inflammatory mediator cascade by reducing TNF-α, IL-1β and IL-6.

The decreased extent of TNF-α and IL-1β had no significant difference ($P>0.05$) , but was significantly different between IL-6 and TNF-α, and between IL-6 and IL-1β ($P<0.01$, Figure 3) in group 4. The data showed that IL-6 decreased more significantly during high-volume CVVH. TNF-α, IL-1β and IL-6 were detectable in the ultrafiltrate.

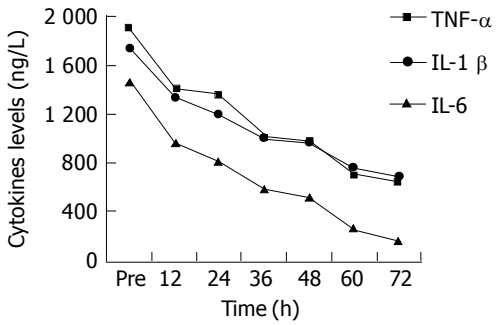

Figure 3 Different cytokine levels in group 4 of acute pancreatitis patients.

Relationship between survival rate and cytokine levels

Before CVVH, serum concentrations of TNF-α and IL-1β had a difference between survival and dead patients (TNF-α $P<0.05$, IL-1β $P<0.05$, Figure 4). TNF-α and IL-1β levels were higher in dead patients. Serum concentrations of TNF-α and IL-1β decreased in both survival and dead patients during CVVH. The decreasing extent of TNF-α and IL-1β was different between survival and dead patients (TNF-α $P<0.05$, IL-1β $P<0.05$). In survival patients, serum concentrations of TNF-α and IL-1β decreased more significantly than that in dead patients (Figure 4). The data demonstrated that survival patients had lower serum levels of TNF-α and IL-1β. Survival rate might be related to the decreasing extent of TNF-α and IL-1β.

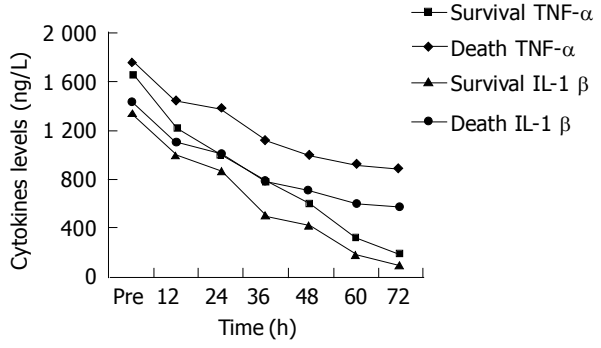

Figure 4 Cytokine levels in survival and dead patients of acute pancreatitis.

DISCUSSION

There is evidence that secondary multiple organ failure resulting from septic complications, is the main cause of mortality in severe pancreatitis. The final pathway of pancreatitis-induced sepsis shares many characteristics with other septic diseases, including systemic histopathological abnormalities, excessive release of pro-and anti- inflammatory cytokines. It has been suggested that patients with severe pancreatitis at the risk to develop septic complications might benefit from early application of CVVH irrespective of the presence of acute renal failure (ARF)[12,13].

Clinical studies have shown that cumulative ultrafiltrate volume is directly correlated with survival rate in patients with sepsis-associated acute renal failure and acute pancreatitis[13,14]. In our study, high-volume CVVH could significantly improve the survival compared to low-volume CVVH. Joannes-Boyau *et al*.[15], evaluated the effect of high volume CVVH on hemodynamic and outcome in patients with septic shock, and found that the mortality in the hemofiltration group decreases significantly. Yekebas *et al*.[16], examined the impact of CVVH on the course of experimental pancreatitis in pigs, and found that the survival time is significantly prolonged by high-volume CVVH. Most likely, this is due to a more effective removal of sepsis mediators. Furthermore, our data show that early CVVH improves survival significantly compared to late CVVH. In a non-randomized trial, it has been hypothesized that early CVVH prior to overt ARF might result in considerable reduction of morbidity in patients with necrotizing pancreatitis[12]. Xie *et al*.[17], studied whether initial time of CVVH could influence survival in acute pancreatitis, and found that the average interval is significantly longer in the mortality group than in the survival group from the onset of acute pancreatitis to CVVH. Yekebas *et al*.[18], reported that animals receiving prophylactic CVVH have a longer survival period, than those receiving CVVH after clinical impairment, suggesting that the improved survival is also due to the fact that early CVVH improves hemodynamic deterioration better than late CVVH. Improved hemodynamic parameters may be due to the application of high-volume CVVH as it was shown in our study. The results are similar to those reported by other studies[15,19]. As Ronco *et al*.[20], argued that it is the time to move from the simple goal of achieving adequate renal support, the proper goal of CVVH in ICU should be multi-organ support therapy.

The resistance of filter membrane was constantly measured by means of the electrical impedance technique during CVVH in the present study. The resistance level reached the plateau at 120 min in 1 000 mL/h filtration rate and at 180 min in 4 000 mL/h filtration rate, respectively. The results demonstrate that the adsorptive saturation time of filter membranes is different in different filtration rate. The adsorptive saturation time of filter membranes is 120 -180 min, if the filtration rate is 1 000-4 000 mL/h. De Vriese *et al*.[21], calculated the cytokine mass balance during hemofiltration in septic patients with acute renal failure, and demonstrated that the adsorption is most prominant immediately after the installation of a new hemofilter (at $t = 1$ and $t = 13$) with a steady decrease thereafter. The

adsorption and the convective elimination increased in a higher blood flow rate and filtration rate. Kellum *et al*.[22], performed CVVH in patients with severe systemic inflammatory response syndrome, and deduced that the adsorptive saturation time of filter membranes is at 6 h after exchanging a new hemofilter by measuring the decreasing extent of serum cytokines. By delivering a large amount of blood per a unit of time or higher transmembrane pressure to push the molecules deeper into the membrane, the adsorptive surface area increases. The higher convection driving force may increase the surface area accessible to adsorption, by pushing the molecules deeper into the hydrogel. In this respect, only minimal adsorption occurs when the ultrafiltrate line is clamped[23]. Therefore, increasing filtration rate can increase the adsorption mass and prolong adsorptive saturation time of filter membranes. Our results showed that serum TNFα concentration decreased significantly in the same group after new filters were installed. After the first, second and third new hemofilters were exchanged, serum TNF-α concentration was negatively correlated with the resistance, demonstrating that the time point at which the resistance reached plateau was the membrane adsorptive saturation time. The resistance could reflect the mass of membrane adsorption of inflammatory mediators. To eliminate more inflammatory mediators, the filter should be changed timely when the filter membrane adsorption is saturated. Compared to that reported by De Vriese *et al*.[21], the method we used to measure the adsorptive saturation time of filter membranes by electrical impedance technique is convenient. The impedance technique has also been used by Rapoza *et al*.[25], to evaluate the permeability of dentin. Several studies have shown that proteins are denatured and desorbed with increasing treatment time[21,24]. Clark *et al*.[26], demonstrated that the desorption of denatured proteins into the blood may be deleterious, indicating that it is very important to change filter timely once filter membrane adsorption is saturated.

In our study, we particularly focused on whether the removal of cytokines, such as TNF-α, IL-1β and, IL-6 was related to different filtration rate and the onset of CVVH. The impact of CVVH on serum cytokine levels is controversial[18,19]. Some investigators have not detected significant decreases of inflammatory mediators in the bloodstream, although relevant concentrations are measured in ultrafiltrate[27,28]. This may be due to the fact that CVVH was performed with low filtration rates. In contrast, De Vriese *et al*.[21], reported that in septic patients with ARF, plasma cytokine levels decrease significantly after hemofiltration and found that there is a close relationship between the filtration rate and the efficiency of CVVH in removing cytokines. Other studies have confirmed the benefits of increasing the filtration rate in terms of improved survival or accelerated recovery from ARF[14,29]. In our study, the filtration rate was 4 000 mL/h which is recommended by Uchino *et al*.[11], as high-volume CVVH. Our data show that high-volume CVVH could eliminate more cytokines than low-volume CVVH. The results are similar to those of some previous clinical studies[17,30]. Watanabe *et al*.[31], found that extremely high interleukin-6 blood levels and bad outcome in critically ill patients are associated with tumor necrosis factor-α and interleukin-1, suggesting that activation of inflammatory mediator is a kind of excessive cascade effect during acute pancreatitis. In the present study, early CVVH decreased serum concentrations of TNF-α, IL-1β, and IL-6 more efficiently than late CVVH, demonstrating that early CVVH can decrease the excessive activation of inflammatory mediator cascade through reduced TNF-α, IL-1β, and Il-6, especially in high CVVH patients. We found that IL-6 decreased more significantly than TNF-α and IL-1β during high-volume CVVH. This may be due to the fact that pro-inflammatory cytokines, such as TNF-α and IL-1β, are removed efficiently by high-volume CVVH and the causative factors increasing the serum IL-6 level are reduced. Gomez-Cambronero *et al*.[1], reported that serum levels of pro-inflammatory cytokines, such as TNF-alpha and IL-1beta, increase during acute pancreatitis and appear to be the driving force for the initiation and propagation of the systemic response. The excessive inflammatory response could be down regulated by removing cytokines and other mediators as Lonneman *et al*.[32], reported. Early CVVH could prevent inflammatory mediators from increasing.

SAP mortality is associated with organ failure. In the early course, organ failure results from inflammatory mediators released by systemic inflammatory response syndrome even in the absence of infection. In the septic phase, since organ failure occurs because of sepsis, it is common in SAP. Inflammatory cytokines play an important role in the progress of acute pancreatitis. In our study, serum concentration of TNF-α and IL-1β decreased more significantly in survival patients than in dead patients 72 h after CVVH, and similar studies in MODS field are available[2,3,5], suggesting that the survival rate is related to the decreasing extent of TNF-α and IL-1β in acute pancreatitis. IL-1β and its mRNA do not exist in the normal pancreas, but are released immediately after pancreatitis is induced. Blockage of the IL-1 receptor significantly decreases intrinsic pancreatic damage and mortality[1,33]. Elevated levels of TNFα may contribute to the pathophysiological sequelae of the disease, and pretreatment with anti-TNFα antibody before induction of the disease can prevent release of TNFα[34], lessen disease severity and increase survival time[35]. Blocking the network of cytokines and eliminating cytokines can improve the prognosis and survival rate of pancreatitis.

In summary, CVVH, especially high-volume CVVH, offers several therapeutic options for patients with acute pancreatitis experiencing multiple organ dysfunction. It can improve the hemodynamic parameters and survival rate of pancreatitis patients by removing inflammatory mediators. CVVH can be performed at the early stage of acute pancreatitis. The adsorptive saturation time of filter membranes is different in different filtration rate. The filter should be changed timely once filter membrane adsorption is saturated.

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