

• CLINICAL RESEARCH •

Clinical effects of continuous high volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome

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Abstract

AIM: To investigate the efficiency of continuous high volume hemofiltration (HVHF) in the treatment of severe acute pancreatitis (SAP) complicated with multiple organ dysfunction syndrome (MODS).

METHODS: A total of 28 SAP patients with an average of 14.36 ± 3.96 APACHE II score were involved. Diagnostic criteria for SAP standardized by the Chinese Medical Association and diagnostic criteria for MODS standardized by American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) were applied for inclusion. HVHF was started 6.0 ± 6.1 (1-30) days after onset of the disease and sustained for at least 72 hours, AN69 hemofilter (1.2 m^2) was changed every 24 hours. The ultrafiltration rate during HVHF was 4 000 ml/h, blood flow rate was 250-300 ml/min, and the substitute fluid was infused with pre-dilution. Low molecular weight heparin was used for anticoagulation.

RESULTS: HVHF was well tolerated in all the patients, and lasted for 4.04 ± 3.99 (3-24) days. 20 of the patients survived, 6 patients died and 2 of the patients quited for financial reason. The ICU mortality was 21.4 %. Body temperature, heart rate and breath rate decreased significantly after HVHF. APACHE II score was 14.4 ± 3.9 before HVHF, and 9.9 ± 4.3 after HVHF, which decreased significantly ($P < 0.01$). Partial pressure of oxygen in arterial blood before HVHF was 68.5 ± 19.5 mmHg, and increased significantly after HVHF, which was 91.9 ± 25 mmHg ($P < 0.01$). During HVHF the hemodynamics was stable, and serum potassium, sodium, chlorine, glucose and pH were at normal level.

CONCLUSION: HVHF is technically possible in SAP patients complicated with MODS. It does not appear to have detrimental effects and may have beneficial effects. Continuous HVHF, which seldom disturbs the hemodynamics and causes few side-effects, is expected to become a beneficial adjunct therapy for SAP complicated with MODS.

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INTRODUCTION

Acute pancreatitis is an inflammatory process of the pancreas with multiple etiologies and a physiopathology that is still unclear. It has a nonspecific clinical presentation, varying from moderate to severe forms, including MODS. The latter is associated with SAP and evolves with high morbidity, mortality and costs^[1,2]. MODS has become the primary cause of death in SAP. From Jan 1997 to May 2002, we accepted 283 patients involved in acute pancreatitis. 11 of 31 cases complicated with MODS died, accounting for 91.7 % of the death toll in acute pancreatitis.

Evidences accumulated over the last years demonstrate that many soluble inflammatory molecules of the systemic inflammatory (and anti-inflammatory) response syndrome (SIRS) can be removed by hemofiltration^[3-5]. This has led to the hypothesis that hemofiltration could play a major role in sepsis therapy as immunomodulatory treatment, in addition to being a blood purification technique. Particular attention has been paid to HVHF to remove inflammatory molecules as compared to standard volume hemofiltration^[6]. HVHF might be of more benefits for amelioration of severe SIRS or MODS, but the clinical feasibility and safety are noticeable. The present study was therefore to investigate the clinical efficacy of continuous HVHF on SAP complicated with MODS.

MATERIALS AND METHODS

Patient population

A total of 28 patients with SAP complicated with MODS, including 7 women and 21 men, with an average age of 51.43 ± 12.96 years were admitted to the study. SAP was diagnosed according to the criteria of Chinese Medical Association for SAP (2001), and MODS was diagnosed according to the criteria of ACCP and SCCM for MODS (1992)^[7]. All the patients had complications such as SIRS, systemic infection, shock, etc (Table 1). The average of APACHE II score was 14.36 ± 3.96 . SAP was caused by alcohol in 5 patients, hyperlipidemia in 3 patients, high fat diet in 3 patients and biliary disease in 17 patients. The CT scan on admission revealed that necrosis of the body of the pancreas was below 33 % in 6 patients, 33-67 % in 12 patients and 67-100 % in 10 patients. The average CT severity score was 8.5 ± 1.4 , and 9 patients were in grade B and 19 in grade C according to Balthazar CT grading criteria of SAP^[8].

Conventional treatment for SAP

Seven patients had accepted surgical treatment in other hospitals before admission to our hospital due to severe complications. All the patients were allocated to ICU and underwent following conventional treatments such as fasting and fluid resuscitation, gastrointestinal decompression, drainage of pancreatic (or bile) duct, and abdominal cavity, oxygen therapy, in which 3 patients underwent mechanical ventilation by non-invasive method and 24 patients underwent mechanical ventilation by tracheotomy, gut cleaning (enema

by taking magnesium sulfate orally), somatostatin, prostaglandin E1, nutritional support (enteral nutrition), antibiotics. 12 patients underwent drainage of peripancreatic abscess and necrosis, and 5 patients who suffered from pancreatitis secondary to biliary disease underwent cholecystectomy.

Table 1 Incidence of complications before HVHF

Complications	Case	Incidence (%)
SIRS ^a	28	100
Systemic infection	10	35.7
ARDS ^a	20	71.4
Shock	14	50.0
Renal failure	7	25.0
Pancreatic encephalopathy	6	21.4
Bleeding in alimentary tract	12	42.8
Cardiac arrhythmia	4	14.3
Heart failure/pulmonary edema	2	7.1
Dysfunction of coagulation	4	14.3
Liver function failure	2	7.1
Fungal infection	7	25.0

SIRS: systemic inflammatory response syndrome; ARDS: acute respiratory distress syndrome.

HVHF technique

For vascular access, a double coaxial lumen 14-Fr catheter was inserted percutaneously either through the right internal jugular or the femoral vein using the Seldinger technique. A Baxter BM25 machine (Baxter, USA) was used for HVHF with a polyacrylonitrile AN69 hemofilter (1.2 m² surface area, 35-kD limit; Hospal, USA). Blood flow was set at 250-300 ml/min and ultrafiltrate flow at 4 000 ml/h, transmembrane pressure was maintained between 300-500 mmHg, and the substitute fluid was infused with pre-dilution. Low molecular weight heparin served as the anticoagulant, patient-activated clotting time was adjusted to 60-70 seconds, a strictly neutral balance was maintained using a digital balance system (Baxter). Elapsed time was expressed in hours from the beginning of HVHF as a T value. T₀ was the beginning of HVHF at zero hours, T₂₄ was 24 hours after T₀, *et al.* These values were recorded for each patient.

Clinical variables

Vital signs, including body temperature, breath rate, blood pressure and heart rate were recorded every half an hour. Blood samples were collected every 24 hours to observe blood cell count, serum amylase and electrolyte, hepatic and renal function, and arterial blood gas. The APACHE II score was applied to evaluate the state of the patients.

Statistical calculations

Results were expressed as mean \pm SD and analyzed using pair-matching *t* test. The difference was considered significant at *P*<0.05.

RESULTS

Outcome

20 patients were cured and discharged from hospital, 6 patients died and 2 patients quit for financial reason. One patient died of pulmonary embolism secondary to the exfoliation of cardiac valve emboli, four of fungal sepsis and one of septic shock. The mortality rate was 21.4 %.

Clinical symptoms and signs

During HVHF the hemodynamics and mean arterial pressure (MAP) were stable, while body temperature, heart rate and breath rate decreased eventually after the beginning of HVHF with amelioration of the symptoms (Table 2). 6 patients suffering from pancreatic encephalopathy secondary to SAP were administrated with 50-100 mg chlorpromazine each day simultaneously, and state of awareness recovered during the procedure with amelioration of dysphoria and delirium. Three of four patients complicated with acute renal failure recovered after HVHF.

Table 2 Changes of vital signs after HVHF

	T ₀	T ₂₄	T ₄₈	T ₇₂	T ₉₆	T ₁₂₀
Case	28	28	28	28	28	28
BT (°C)	37.8 \pm 0.8	37.3 \pm 0.8 ^a	37.2 \pm 0.7 ^a	37.2 \pm 0.8 ^a	37.3 \pm 0.9	37.5 \pm 0.9 ^b
HR (bpm)	127 \pm 23	120 \pm 30	107 \pm 25 ^a	101 \pm 24 ^a	103 \pm 17 ^a	102 \pm 21 ^a
BR (tpm)	31 \pm 5	22 \pm 4 ^a	21 \pm 5 ^a	19 \pm 1 ^a	20 \pm 1 ^a	19 \pm 2 ^a
MAP(kpa)	13.8 \pm 1.9	13.8 \pm 2.0	14.1 \pm 2.3	13.6 \pm 1.7	13.5 \pm 1.7	13.8 \pm 1.8

^a*P*<0.01, vs T₀; ^b*P*<0.05, vs T₀; BT: body temperature (°C); HR: heart rate (beats per minute); BR: breath rate (times per minute); MAP: mean arterial pressure (kpa).

Severity and homeostasis

APACHE II score before HVHF was 14.4 \pm 3.9, and decreased significantly after HVHF, which was 9.9 \pm 4.3 (*P*<0.01, Table 3). Hyperkalemia in two patients and metabolic acidosis in eleven patients were redressed after 24 hours of HVHF. During HVHF the serum potassium, sodium, chlorine, glucose and pH were at normal level.

Table 3 Changes of laboratory parameters after HVHF

Index	Pre HVHF	Post HVHF
Case	28	28
APACHE II score	14.4 \pm 3.9	9.9 \pm 4.3 ^a
PaO ₂	68.5 \pm 19.5	91.9 \pm 25 ^a
CRP	187 \pm 39	87.4 \pm 112
White cell count	15.5 \pm 5.8	14.9 \pm 6.9
Serum amylase	392 \pm 517	103 \pm 184 ^a
Blood urea nitrogen	9.9 \pm 10.1	5.0 \pm 2.9 ^b
Serum albumin	33.0 \pm 5.4	31.8 \pm 4.8

^a*P*<0.01, vs pre-HVHF; ^b*P*<0.05, vs pre-HVHF.

Side-effects correlated with HVHF

Two patients got a high fever caused by infection of intravenous catheter, and recovered after the catheter was removed. Hypophosphatemia occurred in four patients and was redressed by transvenous recruit of compound phosphate solution. The drainage fluid of abdominal cavity of two patients who suffered from intraabdominal hemorrhage became bloody after the beginning of HVHF. Bleeding was controlled following reducing the administration of anticoagulant.

DISCUSSION

With patho-morphological, pathophysiological, biochemical, immunologic and real time imaging observations, adequate evidences have revealed that SAP is a systemic rather than a local critical condition^[9]. Extensive peripancreatic necrosis of fat tissue in the omentum and retroperitoneum may induce a SIRS that extends beyond the pancreas. Hemorrhage is caused

by tissue necrosis or rupture of surrounding blood vessels^[10]. Associated complications include sepsis, MODS, acute respiratory distress syndrome (ARDS), acute renal failure, disseminated intravascular coagulation (DIC), hypovolemic shock, and acute liver failure. MODS has become the primary cause of morbidity and mortality in SAP. Systemic lymphocyte activation (triggered by local release of mediators) causes the distant organ complications in SAP^[11]. Utilizing proteolytic enzymes and toxicant, neutrophils injure the infiltrated vital organs, causing cellular damage and dysfunction of vital organs distant from the pancreas. Multiple organ failure in acute pancreatitis with septic complications can develop, at least in part, by proinflammatory cytokine release and neutrophil activation^[12]. Recent studies have established the critical role played by inflammatory mediators such as TNF α , IL-1 β , IL-6, IL-8, CINC/GRO α , PAF, IL-10, C5a, ICAM-1 and substance P in acute pancreatitis and the resultant MODS^[11-18]. Potentially, there is a therapeutic window between symptom onset and the development of distant organ damage, when anti-inflammatory therapy may be of use. Strategies have been used to target cytokines, such as cytokine antibody, transfection of human anti-inflammation gene and blood purification. Method targeting only one inflammatory mediator is far from combating with complicated cytokines network. Blood purification, such as plasmapheresis, hemadsorption, hemofiltration, can remove nonselective inflammatory mediators, which may make it possible to develop clinically effective anti-inflammatory therapy. Among them, hemofiltration is used widely in clinic.

In 1977, hemofiltration was applied in clinic for the first time to cure the over-hydrated patients resistant to diuretics^[19]. Hemofiltration has been widely applied to patients with MODS as an artificial support such as an artificial kidney or an artificial liver^[20,21]. Recent advances in medical engineering have made it possible to apply hemofiltration continuously (i.e., 24 hours a day, 7 days a week, if necessary) even to critically ill patients, such as MODS patients with renal and hepatic failure^[22]. Continuous hemofiltration (CHF), especially continuous venovenous hemofiltration (CVVH), was developed as continuous renal replacement therapy (CRRT) for patients with severe conditions and has been widely performed mainly in critical care, taking the place of intermittent hemodialysis (IHD). The membrane pore size of a hemofilter used for CHF allows passage of substances ranging from 30 000 to 50 000 Daltons, and the method for solute removal in CHF employs the principle of convection, which is advantageous for removing middle- to high-molecular-weight substances^[20]. Many inflammatory mediators, such as TNF, IL-1, IL-6, sIL-2R, IL-8, IL-2 and IL-10, can be removed by CHF for their molecular weights are under 50 000 Daltons^[6]. Since 1990s, CHF has been employed in treatment of SIRS and MODS secondary to SAP. In 1999, Yekebas^[23] performed experiments in pigs to investigate the effects of CHF on SAP. It was found that effective removal of tumor necrosis factor, phospholipase, and kinin by CHF significantly improved survival time. Animals that received prophylactic CHF had a longer survival period than those in which HVHF was started after clinical onset. Bellomo *et al.*^[24] reported that CHF could remove cytokines from the circulation of septic patients.

There are a large amount of soluble inflammatory mediators in circulation in severe sepsis, so the low intensity therapy, such as standard CRRT at 1 000 ml/h of ultrafiltration rate, would be inadequate. For this reason, many investigators have long felt that if we wish to tackle blood purification therapy in sepsis, we need to move "renal dose" CRRT to "sepsis dose" CRRT. HVHF represents the logical response to these observations^[6]. Rogiers *et al.*^[25] studied the effect of hemofiltration at various levels of intensity and varying times of intervention in dogs made septic by the infusion of

endotoxin. The results suggested that, even at ultrafiltration rates of 3 000 ml/h (close to 7 000-8 000 ml/h in humans), one could achieve clinically important and beneficial hemodynamic effects. Lonnemann *et al.*^[26] were able to demonstrate a beneficial effect of HVHF on macrophage function with restoration of the ability to produce TNF in response to exposure endotoxin. This is the first demonstration that HVHF has an effect on cell function. In the present study we have reported the effects of zero-balanced continuous HVHF on 28 patients suffering SAP complicated with MODS. Body temperature, heart rate, breath rate and APACHE II score decreased significantly and partial pressure of oxygen in arterial blood increased significantly after HVHF. During HVHF the hemodynamics parameters were stable, and serum electrolytes, glucose and pH were at normal level. This investigation established the fact that HVHF was well tolerated in SAP patients complicated with MODS and might be of potential benefits.

Furthermore, hemofiltration might be able to improve organ functions. The study performed by Roman Ullrich^[27] demonstrated that high-volume CVVH improved arterial oxygenation and lung function in endotoxin-induced acute lung injury in pigs. This improvement in arterial oxygenation with CVVH might be due to the removal of interstitial edema, improvement in the microcirculation and uptake of oxygen by parenchymal cells, or it might be due to removal of humoral mediators that depressed oxygen uptake by parenchymal cells. The results clearly indicate that hemofiltration can effectively improve tissue oxygen metabolism. More and more evidences have shown that gut barrier dysfunction is related to multiorgan system failure in sepsis and immune dysregulation^[28,29]. Gut endothelial barrier dysfunction probably plays a central role in the development of the complications of SAP^[30,31]. Pancreatitis-induced hypovolemia due to endothelial barrier leakage and gut arteriovenous shunting could cause intestinal ischemia and reperfusion injury with concomitant gut barrier dysfunction^[32-34]. Hemofiltration can improve the splanchnic vascular infusion, so we might conclude that hemofiltration is helpful to improve the gut barrier function. Improvement of the splanchnic vascular infusion could also decrease the content of endotoxin and the rate of intestinal bacterial translocation in SAP^[35]. Moreover, hemofiltration might play an important role in maintaining the hydrate, electrolyte and acid-base balance and homeostasis, especially when renal function was injured.

In summary, HVHF is technically possible in patients suffering from SAP complicated with MODS. It does not appear to have detrimental effects and may have beneficial effects. Continuous HVHF, which seldom disturbs the hemodynamics and causes few side-effects, offers therapeutic options for SAP complicated with MODS. The mechanisms underlying HVHF in SAP are thus complex and yet not fully elucidated.

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