Effects of time interval for hemofiltration on the prognosis of severe acute pancreatitis

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Abstract
AIM: To evaluate the impact of time interval for hemofiltration (HF) on the prognosis of severe acute pancreatitis (SAP).

METHODS: Thirty-six consecutive patients with severe acute pancreatitis were included in the study. Atlanta classification system was applied for stratification. They were randomly divided into short veno-venous HF group (SVVH, Group 1, 20 patients); and long veno-venous HF group (LVVH, Group 2, 16 patients). In Group 1, SVVH was stopped when the abdominal signs disappeared, and heart rate and breath rate were less than 90 beats/min and 20 times/min, respectively. HF was stopped if SVVH was continued, and when heart rate and breath rate were more than 90 beats/min and 20 times/min again (Group 2). Except that the time interval for HF was different, other parameters for HF were the same. And conservative curing rate, survival rate, cost for hospital stay and length of hospital stay were observed.

RESULTS: Time interval for HF in Group 1 (3.8±1.3 hr) was shorter than that of in Group 2 (9.3±2.9 hr), P<0.01. Conservative curing rate (90%) in Group 1 was much higher than that in Group 2 (56.3%) (P<0.05); but cost in Group 1 (RMB 56 600±56 400 Yuan) was lower than that in Group 2 (RMB 137 000±105 000 Yuan) (P<0.05). And the survival rate (95%) in Group 1 was higher than that in Group 2 (81.3%) (P<0.05); however, hospital stay in Group 1 (44.3±41 days) was shorter than that in Group 2 (55.2±39.5 days) (P<0.05). So, the prognosis was not improved through the prolongation of time interval for HF, but side-effects were seen.

CONCLUSION: The prognosis was not further improved by LVVH in the treatment of SAP, with side-effects. Time interval for HF plays an important role in treatment of SAP in early stage. SVVH is thought to be superior to LVVH; and LVVH is superior to CVVH in early treatment of SAP.

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INTRODUCTION
Up to date, strategies of treatments of severe acute pancreatitis have been extensively developed, such as prolongation of operation; peritoneal lavage, blood purification, and continuous arterial infusion of protease inhibitor, endotelin receptor antagonist to reduce capillary leakage, and so on, in addition to intensive care. But the mortality of SAP is still about 15-25%. So, how to further raise the survival rate is most difficult. A large amount of cytokines released from activated macrophages and other sites as well as cytokines cascades play an important role in deteriorating the disease.

Clinical and experimental data suggest that hemofiltration might be of benefit for amelioration of severe systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction and prevention of pancreatic necrosis. Our data showed that pancreatic necrosis was prevented, and the prognosis was ameliorated through short veno-venous hemofiltration (SVVH). However, it is reported that better efficacy was also obtained from continuous veno-venous hemofiltration (CVVH). The aim of the present study is therefore to investigate the time interval of hemofiltration, by prolonging the time interval for HF in order to observe its impact on clinical efficacy.

MATERIALS AND METHODS

Patients and groups
Patients Thirty-six consecutive patients with SAP admitted to Ruijin Hospital, Shanghai, China from April 1997 to May 2002, were included in the study. Prior to study, all patients themselves or their relatives had been informed in detail, and agreement was obtained. Atlanta classification system was applied for stratification of patients with SAP. Criteria for the study were APACHE II score more than 8, with dysfunction of one or more organs, within 72 hours after onset of the disease and no indication for operation temporarily. There were 25 men and 11 women, aged from 18 - 82 years. Etiologies included hyperlipidemia (26 cases) with significantly increased triglyceride and biliary disease (10 cases).

Groups The patients were divided randomly into short veno-venous hemofiltration group (Group 1, SVVH) and long veno-venous hemofiltration group (Group 2, LVVH). In Group 1, consisted of 20 patients, 16 men and 4 women; aged 52.4±14.2 years, including 14 with hyperlipidemia, 1 with hyperlipidemia and alcoholic abuse, and 5 with biliary disease; In Group 2 was made up of 16 patients, 12 men and 4 women, aged 45.1±9.2 years, including 11 patients with hyperlipidemia and 5 with biliary disease; and the time interval for HF ranged from 5-20 hours.

APACHE II scores were 13.9±3.8 and 12.1±4.2 in the two groups; and there was no difference (P>0.05) before hemofiltration.

Methods
Hemofilters HF was performed using Diapact CRRT machine from B.Braun Co, Germany. And filters used for HF were polysulphone filters (Fresenius Medical Care, AV 600 S, with the cutoff of molecular weight of 30 KD); and extracorporeal lines were primed with one liter of hapatrinized saline (5 000 IU/L). Vascular access was obtained by two Gambro catheters inserted into each femoral vein. Low molecular weight heparin (Fragmin, 5 000/ampule) was administered at dose of 100-140 IU/kg, and bolus injection was made before HF.
Ultrafiltrate was replaced with substitute made according to electrolyte and blood glucose. Pre-dilution mode was used. Extracorporeal blood flow ranged from 250 to 360 ml/min. Ultrafiltrating rate was controlled within 50-300 ml/h.

Indication for stopping HF
In group 1, SVVH was stopped when the abdominal signs disappeared, and heart rate and breath rate were less than 90 beats/min and 20 times/min, respectively. HF was stopped if SVVH was continued when heart rate as well as breath rate were more than 90 beats/min and 20 times/min again (Group 2).

Follow-up
CT scanning was done every month; and intra-pancreatic as well as extra-pancreatic changes were analyzed.

Prognostic indices
Conservative curing rate, hospital stay, cost and survival rate were analyzed. The conservative cure referred to intra-pancreatic and extra-pancreatic lesions absorbed entirely and/or formed into pseudocyst without symptoms.

Statistical calculations
Data were reported as mean ± standard deviation, and analyzed using Student’s t and or qi square.

RESULTS
Time interval
Time interval for HF was 3.81±1.3 hrs in Group 1 and 9.38±2.9 hrs in Group 2, P<0.05.

Comparison of parameters of SVVH and LVVH
There was no difference in age, beginning time for HF, APACHEII scores before HF, substitute rate, blood flow and ultrafiltrate rate between the two groups, (Table 1).

| Parameters          | Group 1 (5-20 h) | Group 2 (5-20 h) | P values |
|---------------------|------------------|------------------|----------|
| Number              | 20               | 16               |          |
| Age (years)         | 52.4±4.2         | 45.1±9.2         | >0.05    |
| APACHEII before HF  | 13.9±3.8         | 12.1±4.2         | >0.05    |
| Beginning time (hr) | 45.9±21.2        | 37.4±22.5        | >0.05    |
| Rate of substitute (ml/h) | 2700±500 | 2880±500        | >0.05    |
| Blood flow (ml/min) | 200–250          | 250–360          | >0.05    |
| Rate of ultrafiltrate (ml/h) | 342.5±251 | 240±27        | >0.05    |
| Time interval (hr)  | 3.8±1.3          | 9.38±2.9         | >0.01    |
| Colloid volume (ml) | 700±258.2        | 1500±852.9       | >0.01    |
| The amount of heparin (IU) | 7700±2341.1 | 12000±6000      | >0.01    |
| Substitue volume (L) | 9.5±3.2         | 35.1±6.5         | >0.01    |
| Ultrafiltrate volume (ml) | 1040±520 | 2400±700        | >0.01    |
| Filters             | 1.44±0.73        | 2.75±1.4         | >0.05    |

Prognosis
Conservative curing rate was more significantly increased in Group 1 than in Group 2, P<0.05; but cost was significantly decreased, P<0.05, (Table 2).

| Parameters          | Group 1 (<5 h) | Group 2 (5-20 h) | P values |
|---------------------|----------------|------------------|----------|
| Conservative curing rate (%) | 90% (19/20) | 56.3% (9/16) | <0.05    |
| Survival rate (%)   | 95% (19/20)   | 81.3% (13/16)    | <0.25    |
| Cost (×10⁶ yuan)    | 5.66±6.6      | 13.7±10.5        | <0.05    |
| Hospital stay (d)   | 44.3±17.3     | 55.2±29.5        | <0.2     |

DISCUSSION
Up to date, strategies have been used to target cytokines, such as cytokine anti-body, purification and transient transfection of human IL–10 gene. In term of neutralization of antibody, for example, Hughes[8,9] reported that scores for pathology of pancreas were significantly improved by TNFα blockade. But, the method is only one antibody to one antigen to neutralize cytokine, and it is far from combating with complicated cytokines network. According to Grewal[21] and Kingsnorth[19], despite amelioration of ascites production by TNFα blockade, histologic evaluation scoring was not statistically different. And IL–1r antagonist only modified the changes in vital organs induced by SAP[22], it did not affect the degree of local pancreatic insult. This method is controversial and has not been reported in clinical trial till now. Denham[21] demonstrated that transient transfection of a human IL–10 gene decreased the severity of pancreatitis during acute inflammatory process. It is only an animal experiment, that blood purification[14,18,24], such as plasmapheresis, hemadsorption, hemofiltration, can remove the mediators from circulation. Among them, hemofiltration is used widely in clinics.

In 1991, Blinzer reported that CVVH can be used to treat SAP at early stage[18], although no organ failure happened. This is the earliest report of CVVH to blockade pancreatic necrosis. In 1994, Gehbart[5] reported that CVVH was applied to 11 patients with most serious clinical course and multi-system failure. The overall lethality rate of the treated patients was 7.9 %. In 1998, Schmidt[25] suggested that CVVH had been proven to be of no efficacy. In 1999, Yekebas[26] performed animal experiment to investigate the effects of CVVH on SAP, showing that the survival time was significantly prolonged. In 2001, Pupelis[26] applied that hemodialysis, hemofiltration, plasmapheresis, hemadsorption to SAP patients concomitant with organ failure, and achieved a good result.

These investigations have shown that CVVH is of benefit for treatment of SAP or multiple organ dysfunction secondary to SAP. We performed SVVH within 72 hours after onset of the disease, and obtained satisfactory clinical efficacy[17]. The present study showed that survival rate in Group 1 was 95 %, which was much higher than that of 92 % from the 11 patients in Gehbart’s report[5]. Pupelis[26] reported a survival rate of 80 % using CVVH and hemodialysis to treat SAP, which is the same as that of non-hemofiltration[14]; and its conservative curing rate (38.2 %,13/34) is much lower than ours (90 %,19/20), (χ²=13.8, P<0.002). Miller[27] reported a survival rate of only 71.4 % (5/7) using CVVH to treat SAP. It is much lower than ours (95 %, 19/20), (χ²=2.917, P=0.088). In the present study, the conservative curing rate, cost, hospital stay and survival rate were improved in SVVH group as compared with LVVH group. The conservative curing rate and cost were especially improved significantly (P<0.05). Why is the efficacy decreased in LVVH group or CVVH group?
In the early stage of SAP, pro-inflammatory and anti-inflammatory cytokines are inter-related in a united entity under pathological state. Any of them which is over-produced or less-produced, will contribute to different pathophysiological response, such as systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS), Mixed antagonist response syndrome (MARS)\(^{[28,29]}\). According to this assumption, pro-inflammatory and anti-inflammatory cytokines should be in a dynamic balance state through cytokines eliminated partly. The pro-inflammatory and anti-inflammatory level was modulated through 4h-SVVH\(^{[31]}\); the former (TNF, IL-1, IL-8, IL-6 and sIL-2R) was decreased and the latter (IL-2, IL-10) was increased. Monocyte cytokine (TNF, IL-6, IL-8) production was increased in association with systemic complications in acute pancreatitis\(^{[30]}\); and IL-10 prevented pancreatic necrosis\(^{[31,32]}\) as well as death in lethal necrotizing pancreatitis\(^{[33]}\). SIRS was doomed to be interrupted and the severity of SAP was decreased significantly. This demonstrates that dynamic balance of pro- and anti-inflammatory cytokines is established at the pathological state. When T and B lymphocytes and monocytes are activated, membrane receptor of IL-2 would be expressed; and soluble receptor of IL-2 (sIL-2R) is liberated into circulation\(^{[34]}\). Simultaneously, sIL-2R can combine with IL-2; and if it is over produced, serum level of IL-2 will be decreased. It is reported that IL-2 production was decreased in acute pancreatitis\(^{[35]}\). And IL-2 is the major factor that activated T and B lymphocytes and decreased infection rate\(^{[36]}\). Therefore, over-produced sIL-2R may lead to decreased immune function. In clinical trial\(^{[37]}\), serum level of sIL-2R was decreased significantly through SVVH, however, serum concentration of IL-2 was increased, and the infection rate was decreased. At the same time, the time of infection occurrence was postponed, suggesting that immune function has been up-regulated. CVVH may contribute to immune-paralysis due to over-removed cytokines and inhibit the up-regulation of PMN phagocytosis capacity after intra-abdominal sepsis\(^{[37]}\). Thus, dynamic balance obtained between pro-inflammatory cytokines and anti-inflammatory cytokines is imbalanced again. So, there is no difficulty in understanding increased infection and earlier operation in LVVH group.

During conservative treatment, two factors, immune function of body and optimal application of antibiotics, are important in the prevention of pancreatic infection. Ciprofloxacin and Metronidazole were infused to 36 patients on admission. If the body temperature was increased, carpenemns plus fluconazol would be infused empirically. Simultaneously, body fluids were cultured. If the temperature was controlled, antibiotics were not stopped until the enteral nutrition had been fed for one week. On the contrary, antibiotics were changed according to the cultures. Given temperature was still abnormal through optimal antibiotics and strengthened immune function, and infection in other sites was excluded, drainage of infected necrotic pancreata should be performed. This demonstrated that pancreatic infection had not been controlled by intensive treatments from 48 to 72 hours.

In Group 1, pseudocysts were entirely absorbed from 2 months to 2 years in 15 patients, and 3 patients underwent jejuno-pseudocyst Roux-en-Y anastomosis or gastropseudocyst anastomosis. Seven patients underwent drainage within 20 to 30 days after onset of the disease in Group 2.

According to our clinical trial, once indices for cessation of hemofiltration were reached, it should be stopped immediately. Additionally, although indices for stopping HF has not been reached with more than 8 h-HF, hemofiltration should also be stopped as we seek other factors leading to the change of heart rate and breath rate, because they may be affected by other factors.

On admission, patients should be strictly estimated that whether he or she has the indication for SVVH. If he or she is below 70 years old, time is within 72 hours after onset of the disease and without billiary obstruction, it is wise to perform SVVH. It did not reach the peak of the disease until the time interval for abdominal pain was 72 hours. Within 72 hours, cascades of cytokines were blocked easily, and vicious cycle was not formed between secondary chemokines released\(^{[38]}\) and cytokines. Thus, 72 hours should be emphasized heavily. And the earlier the hemofiltration began, the better the result was. Patients with ACST underwent operation, EST or nasobiliary catheter inserted to drain bile. SVVH could still be performed after these.

Although prognosis was improved through SVVH, it is only a new method in synthetical treatment strategies for SAP. It can not replace other measures. For example, Pixiao (a traditional Chinese medicine) is applied continuously to the whole abdomen after hemofiltration is stopped, and until it has no effects.

In summary, SVVH is superior to LVVH, and LVVH is better than CVVH in the treatment of SAP in early stage. Much more significant side-effects occurred due to longer time interval for HF.

REFERENCES

1. Hartwig W, Maksan SM, Foltzik T, Schmidt J, Jerfathr C, Klar E. Reduction in mortality with delayed surgical therapy of severe acute pancreatitis. J Gastrointest Surg 2002; 6: 481-487
2. Gebhardt C, Bodeker H, Blinzler L, Kraus D, Hergott G. Changes in therapy of severe acute pancreatitis. Chirurg 1994; 65: 33-40
3. Yamauchi J, Takeda K, Shibuya K, Sunamura M, Matsuno S. Continuous regional application of protease inhibitor in the treatment of acute pancreatitis. An experimental study using closed duodenal obstruction model in dogs. Pancreatology 2001; 1: 662-667
4. Elbl G, Buhr HJ, Foltzik T. Therapy of microcirculatory disorders in severe acute pancreatitis: what mediators should we block? Intensive Care Med 2002; 28: 139-146
5. Bank S, Singh P, Pooran N, Stark B. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. J Clin Gastroenterol 2002; 35: 50-60
6. Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. Am J Surg 1998; 175: 76-83
7. Van Laethem, Eskinazi R, Louis H, Richaert J, Bobberecht P, Deviere. Multisystemic production of interleukin 10 limits the severity of acute pancreatitis in mice. Gut 1998; 43: 408-413
8. Hughes CB, Gabor LW, Mohey el-Din AB, Mott L, Gabor AO. Anti-TNF therapy improves survival and ameliorates the pathophysiologic sequelae in acute pancreatitis in the rat. Am J Surg 1996; 171: 274-280
9. Hughes CB, Gabor LW, Mohey el-Din AB, Mott L, Gabor AO. Inhibition of TNF improves survival in an experimental model of acute pancreatitis. Am J Surg 1996; 62: 8-13
10. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. Gut 1997; 40: 1-4
11. Osman MO, Gesser B, Mortensen JT, Matsushima K, Jensen SL, Larsen CG. Profiles of pro-inflammatory cytokines in the serum of rabbits after experimentally induced acute pancreatitis. Scand J Gastroenterol 1998; 33: 50-60
12. Odal A, Hirasawa H, Shiga H, Nakashiki K, Matsuda K, Nakamura M. Continuous hemofiltration/ hemodialfiltration in critical care. Ther Apher 2002; 6: 193-198
13. Gotlib L, Barzilay E, Shustak A, Wais Z, Jaichenko J, Lev A. Hemofiltration in septic ARDS. The artificial kidney as an artificial endocrine lung. Resuscitation 1986; 13: 123-132
14. Gotlib L, Shustak A, Lev A, Fudin R, Jaichenko J. Treatment of surgical and non-surgical septic multiple organ failure with bicarbonate hemodialysis and sequential hemofiltration. Int Care Med 1995; 21: 104-111
15. Barzilay E, Kessler D, Berlot G, Gullo A, Geber D, Ben Zeev I. Use of extracorporeal supportive techniques as additional treatment for septic-induced multiple organ failure patients. Crit Care Med 2002; 30: 1288-1295
Bradley EL 3rd

C. Conservative treatment of severe necrotizing pancreatitis. Summary of the international symposium on acute experimental pancreatitis in pigs. Stummvoll HK, eds. Continuous hemofiltration. In: Sieberth HG, Mann H, Blinzler L. Hemofiltration attenuates polymorphonuclear leukocyte phagocytosis in porcine intra-abdominal sepsis. Adv Surg 1999; 32B: 61-76.

Blinzler I, Häusler J, Bodeker H, Zauke U, Martin E, Gebhardt C. Conservative treatment of severe necrotizing pancreatitis using early continuous veno-venous HF. In: Sieberth HG, Mann H, Stummvoll HK, eds. Continuous hemofiltration. Contrib Nephrol 1991; 93: 234-236.

Yekebas EF, Treede H, Knoefel WT, Bloechle C, Fink E, Izbicki JR. Influence of zero-balanced hemofiltration on the course of severe experimental pancreatitis in pigs. Ann Surg 1999; 229: 514-522.

Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis. Atlanta, Ga, September 11 through 13, 1992. Arch Surg 1993; 128: 586-590.

Grewal HP, Mohey el Din A, Gaber L, Kotb M, Gaber O. Amelioration of the physiologic and biochemical changes of acute pancreatitis using an anti-TNFα polyclonal antibody. Am J Surg 1994; 167: 214-219.

Tanaka N, Murata A, Uda K, Uda Ki, Toda H, Kato T, Hayashida H, Matsuura N, Mori T. Interleukin-1 receptor antagonist modifies the changes in vital organs induced by acute necrotic pancreatitis in a experimental model. Crit Care Med 1995; 23: 901-908.

Denham W, Denham D, Yang J, Carter G, Mackay S, Moldawer LL, Carey LC, Norman J. Transient human gene therapy. A novel cytokine regulatory strategy for experimental pancreatitis. Ann Surg 1998; 227: 812-820.

Belomo R, Tipping P, Boyce N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. Crit Care Med 1993; 21: 522-526.

Schmidt J, Werner J. Acute pancreatitis: reliable and prospective conservative therapy. Langenbecks Arch Chir Suppl Kongressbd 1998; 115: 434-438.

Pupelis G, Austrums E, Snippe K. Blood purification methods for treatment of organ failure in patients with severe pancreatitis. Zentral Chir 2001; 126: 780-784.

Miller BJ, Henderson A, Strong RW, Fielding GA, DL Marco AM, O’Loughlin BS. Necrotizing pancreatitis: operating for life. World J Surg 1994; 18: 906-911.

Davies MG, Hagen PO. Systemic inflammatory response syndrome. Br J Surg 1997; 84: 920-935.

Bone RC. Sir Isaac Newton, Sepsis, SIRS and Cars. Crit Care Med 1996; 24: 1125-1127.

McKay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complications in acute pancreatitis. Br J Surg 1996; 83: 919-923.

Van Laethem J, Marchant A, Delvaux A, Goldman M, Robberecht P, Veer T, Deviere J. Interleukin 10 prevents necrosis in murine experimental acute pancreatitis. Gastroenterology 1995; 108: 1917-1922.

Rongione AJ, Kusske AM, Kwan K, Ashley SW, Reber HA, Mcdadden DW. Interleukin-10 reduces the severity of acute pancreatitis in rats. Gastroenterology 1997; 112: 960-967.

Kusske AM, Rongione AJ, Ashley SW, Mcdadden DW, Reber HA. Interleukin-10 prevents death in lethal necrotizing pancreatitis in mice. Surgery 1996; 120: 284-289.

Salomone T, Boni P, Serra C, Moriselli-Labate AM, Di Gioia AL, Rombo M, Guariento A. The soluble interleukin-2 receptor, peripheral blood, and reticulocyte fractions in acute pancreatitis. Int J Pan 1996; 20: 197-203.

Curley P, Nestor M, Collins K, Saporschetz I, Mendez M, Mannick JA, Rodrick M. Decreased Interleukin-2 production in murine acute pancreatitis: potential for immunomodulation. Gastroenterology 1996; 110: 583-588.

Kusske AM, Rongione AJ, Reber HA. Cytokine and acute pancreatitis. Gastroenterology 1996; 110: 639-642.

Discipio AW, Burchard KW. Continuous Arteriovenous Hemofiltration attenuates polymorphonuclear leukocyte phagocytosis in porcine intra-abdominal sepsis. Ann Surg 1997; 213: 174-180.

Grady T, Liang P, Ernst SA, Logsdon CD. Chemokine gene expression in rat pancreatic acinar cells is an early event associated with acute pancreatitis. Gastroenterology 1997; 113: 1966-1975.

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