PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2005;11(1):127-131
World Journal of Gastroenterology ISSN 1007-9327


• BASIC RESEARCH •

# Amelioration of hemodynamics and oxygen metabolism by continuous venovenous hemofiltration in experimental porcine pancreatitis

Hao Wang, Zhen-Huan Zhang, Xiao-Wen Yan, Wei-Qin Li, Da-Xi Ji, Zhu-Fu Quan, De-Hua Gong, Ning Li, Jie-Shou Li

**Hao Wang, Zhen-Huan Zhang, Xiao-Wen Yan, Wei-Qin Li, Zhu-Fu Quan, Ning Li, Jie-Shou Li,** Department of Nephrology, Nanjing University School of Medicine, Nanjing 210093, Jiangsu Province, China
**Da-Xi Ji, De-Hua Gong,** Department of Surgery, Nanjing University School of Medicine, Nanjing 210093, Jiangsu Province, China
**Supported by** the Social Development Foundation of Jiangsu Province, No. BS2000051
**Correspondence to:** Dr. Wei-Qin Li, Department of Surgery, Jinling Hospital, 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China. liweiqin@jlonline.com
**Telephone:** +86-25-3685194 **Fax:** +86-25-4803956
**Received:** 2004-03-06 **Accepted:** 2004-04-29

## Abstract

**AIM:** To investigate the potential role of continuous venovenous hemofiltration (CVVH) in hemodynamics and oxygen metabolism in pigs with severe acute pancreatitis (SAP).

**METHODS:** SAP model was produced by intraductal injection of sodium taurocholate [4%, 1 mL/kg body weight (BW)] and trypsin (2 U/kg BW). Animals were allocated either to untreated controls as group 1 or to one of two treatment groups as group 2 receiving a low-volume CVVH [20 mL/(kg·h)], and group 3 receiving a high-volume CVVH [100 (mL/kg·h)]. Swan-Ganz catheter was inserted during the operation. Heart rate, arterial blood pressure, cardiac output, mean pulmonary arterial pressure, pulmonary arterial wedge pressure, central venous pressure, systemic vascular resistance, oxygen delivery, oxygen consumption, oxygen extraction ratio, as well as survival of pigs were evaluated in the study.

**RESULTS:** Survival time was significantly prolonged by low-volume and high-volume CVVHs, which was more pronounced in the latter. High-volume CVVH was significantly superior compared with less intensive treatment modalities (low-volume CVVH) in systemic inflammatory reaction protection. The major hemodynamic finding was that pancreatitis-induced hypotension was significantly attenuated by intensive CVVH (87.4±12.5 kPa *vs* 116.3±7.8 kPa, $P<0.01$). The development of hyperdynamic circulatory failure was simultaneously attenuated, as reflected by a limited increase in cardiac output, an attenuated decrease in systemic vascular resistance and an elevation in oxygen extraction ratio.

**CONCLUSION:** CVVH blunts the pancreatitis-induced cardiovascular response and increases tissue oxygen extraction. The high-volume CVVH is distinctly superior in preventing sepsis-related hemodynamic impairment.



**Key words:** Pancreatitis; Continuous venovenous hemofiltration; Hemodynamics; Oxygen metabolism

Wang H, Zhang ZH, Yan XW, Li WQ, Ji DX, Quan ZF, Gong DH, Li N, Li JS. Amelioration of hemodynamics and oxygen metabolism by continuous venovenous hemofiltration in experimental porcine pancreatitis. *World J Gastroenterol* 2005; 11(1): 127-131
http://www.wjgnet.com/1007-9327/11/127.asp

## INTRODUCTION

Acute pancreatitis may lead to non-infectious systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS). Similar to infectious SIRS or sepsis[1], this inflammatory response reflects the activation of humoral and cellular inflammatory cascades and may be accompanied with alterations in the oxygen extraction capabilities of tissue and hyperdynamic cardiovascular failure[2]. Notably, small to middle-sized molecules, such as proinflammatory cytokines or activated complement factors seem to play a key role as humoral mediators in the development of SIRS and MODS[3,4]. Since MODS is a leading cause of morbidity and mortality in surgical intensive care, attenuation of SIRS by antagonizing[5,6] or removing[7] potentially involved mediators has attracted great interest as a supportive strategy to prevent organ failure in critically ill patients. Unfortunately, therapeutic interventions aiming at neutralizing or antagonizing individual inflammatory cytokines have generally been disappointing[8,9]. Although anti-mediator strategies are successful in experimental models of endotoxemia, there is an increasing body of evidence that proinflammatory mediators are crucial to mount a local host defense response in addition to their systemic toxic effects[10,11]. Moreover, simultaneous production of a wide variety of inflammatory mediators sharing many biological activities may limit the use of strategies directed against a single mediator[12].

Hemofiltration, especially continuous venovenous hemofiltration (CVVH), is a safe and well established treatment in critically ill patients with renal failure, and has also been used in the treatment of severe acute pancreatitis (SAP), acute respiratory distress syndrome (ARDS) and sepsis[13,14]. Although many inflammatory mediators involved in the development of SIRS, ARDS and MODS are known to have a molecular weight well below the cut-off value of hemofiltration membranes, the use of CVVH to attenuate SIRS by eliminating a broad spectrum of small to middle-sized inflammatory mediators has been a source of considerable controversy[7,13,15-17]. In particular, potential targeting of multiple mediators that are released into the systemic circulation without affecting the local host response by CVVH is intriguing. However, prospective, randomized and controlled basic studies assessing the potential effects of hemofiltration on hemodynamics and oxygen metabolism in animals with severe SIRS, septic shock or multiple organ failure are sparse.

The aim of the present study was therefore to investigate the influence of prophylactic CVVH on the development of MODS in pigs with severe acute pancreatitis.

## MATERIALS AND METHODS

### *Anesthesia and surgical preparation*

Twenty-four fasted domestic pigs (body weight [BW] 21-30 kg) were premedicated intramuscularly with ketamine (10 mg/kg) and atropine (0.06 mg/kg). Adequate anesthetic depth was achieved by continuous intravenous application of pentothal sodium [6 mg/(kg·h)]. After endotracheal intubation, the animals were ventilated mechanically with air. The ventilation rate was 12 breaths/min, and the respiratory tidal volume was set to 8 mL/kg BW. For the duration of the experiments, all animals received a 0.9% NaCl infusion at a rate of 5 mL/kg per hour. After the instrumentation of the animals by arterial and Swan-Ganz catheters, mean arterial blood pressure (MAP), central venous pressure (CVP), and heart rate (HR) were monitored continuously. Systemic vascular resistance (SVR) and cardiac index (CI) were calculated intermittently.

### Induction of pancreatitis

Pancreatitis was induced by pressure-controlled (100 mmHg), intraductal infusion of sodium taurocholate[18] (4%, 1 mL/kg BW, Sigma Chemical, Germany) and trypsin (2 U/kg BW, Difco Chemical, USA). Control animals ($n$ = 8, group 1) underwent the spontaneous course of the disease without any treatment. In two treatment groups, different volumes of CVVH were applied simultaneously with the induction of pancreatitis.

### Hemofiltration

The 16 pigs randomized to receive CVVH were cannulated with a venous double-lumen catheter via a central vein to allow pumps driving venovenous hemofiltration. Zero-balanced CVVH was performed with a blood flow rate of 80 mL/min in a predilution mode using a polyacrylonitrile membrane (AN69, Hospal, France) connected to a continuous blood pump (Baxter, USA). The filters were replaced daily. To avoid clotting of the dialyzer, heparin was added into the inflow line of the extracorporeal circuit in pigs subjected to CVVH. Group 2 animals ($n$ = 8) underwent a filtration turnover of 20 mL/(kg·h) and group 3 ($n$ = 8) underwent a filtration turnover of 100 mL/(kg·h). After a maximal observation period of 72 h, animals were killed.

### Measurements

Blood samples were taken throughout the whole study period for evaluation of blood gases, blood cell counts and chemistry. From the induction of pancreatitis (at the time of the induction; "time 0") up to 72 h after induction, the following variables were recorded: heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), cardiac output (CO), systemic vascular resistance (SVR), arterial oxygen content ($CaO_2$), mixed venous oxygen content ($CvO_2$), and body temperature (BT). Cardiac index (CI), oxygen delivery ($DO_2$), oxygen consumption ($VO_2$) and oxygen extraction ratio (OER) were calculated from CO, $CaO_2$ and $CvO_2$ according to the following equations: $DO_2$ [mL/(min·m$^2$)] = CI [l/(min·m$^2$)]×$CaO_2$[mL/100mL]×10, $VO_2$= CI [l/(min·m$^2$)]×($CaO_2$[mL/100mL]-$CvO_2$[mL/100mL])×10, and OER= $VO_2$/$DO_2$.

### Statistical analysis

Data were expressed as mean±SD. Normal distribution of data was tested using the Kolmogorov-Smirnov test. Statistical differences of baseline values *vs* changes of parameters after pancreatitis were evaluated by one-way analysis of variance for repeated measures. Differences between the treatment groups were determined by analysis of variance, followed by the Scheffe test when significant differences were found. $P$ less than 0.05 was considered statistically significant.

## RESULTS

### Survival

Compared with control animals, those that received CVVH significantly prolonged their survival time. In addition, high-volume CVVH prolonged survival significantly compared with low-volume CVVH. The respective mean survival time was 31.1±6.8 h for control group (group 1) ($P$<0.05 *vs* groups 2 and 3), 40.0±6.7 h for low-volume CVVH (group 2) ($P$ = 0.001 *vs* group 3), and 57.8±10.3 h for intensive (high-volume) CVVH (group 3), respectively.

### Hemodynamics and clinical parameters

After the onset of pancreatitis, group 1 (control) animals showed an early phase hyperdynamic response characterized by increase in heart rate, and body temperature ($P$<0.01, Table 1), cardiac index ($P$<0.01, Table 2), and rapid decrease in MAP and SVR ($P$<0.01, Table2). In the late phase of septic macrocirculatory derangement, a dramatic breakdown of the entire macrocirculation and a decrease in body temperature occurred. The major reason was a progressive cardiac insufficiency indicated by a decrease in cardiac index ($P$ <0.01, Table 2). CVVH led to a reversal of hemodynamic impairment that resulted eventually in significantly prolonged survival in both the treatment groups. Both the initial elevation of body temperature up to almost 41 ℃ and the hypothermia in the late course of experiments were significantly ameliorated by CVVH. The high-volume CVVH was distinctly superior in preventing sepsis-related hemodynamic impairment compared with the low-volume group.

### Oxygen delivery and consumption

In early phase of pancreatitis, $DO_2$ was found to be significantly

**Table 1** Clinical parameters (mean±SD)

| Parameter | Group | Baseline | 6 h | 12 h | 24 h | 36 h | 48 h |
|---|---|---|---|---|---|---|---|
| HR(bpm) | 1 | 123.0±8.2 | 179±9.7$^d$ | 194±20.8$^d$ | 164±26.2$^c$ | 132±23.0 | NC |
| | 2 | 123.0±8.2 | 159±10.4$^{ad}$ | 165±15.5$^{ad}$ | 159±21.6$^d$ | 139±25.2 | 141±36.1 |
| | 3 | 125.0±8.3 | 149±9.9$^{ad}$ | 155±23.8$^{ad}$ | 148±21.4$^d$ | 148±17.6$^d$ | 138±18.4 |
| BT(°C) | 1 | 37.1±1.2 | 39.6±1.1$^d$ | 40.0±0.9$^d$ | 36.0±0.6$^c$ | 35.6±0.6 | NC |
| | 2 | 37.9±0.7 | 38.7±1.2 | 38.7±0.6$^a$ | 36.8±1.2$^c$ | 36.1±1.3 | 37.5±3.4 |
| | 3 | 37.8±0.5 | 38.3±0.6$^{ac}$ | 38.6±0.8$^a$ | 38.8±0.8$^{ac}$ | 38.5±0.2$^{ac}$ | 39.0±0.3 |
| Amy(U/l) | 1 | 238.3±122.6 | 3 635.0±427.2$^d$ | 9 535.8±5 802.6$^d$ | 7 535.7±6 573.6$^c$ | 5 502.7±1 976.8$^c$ | NC |
| | 2 | 336.0±123.8 | 3 309.1±1331.2$^d$ | 8 199.4±5 881.0$^d$ | 8 441.8±5 730.6$^d$ | 2 960.5±1 292.6$^c$ | 3 168.5±1 136.3 |
| | 3 | 237.0±66.7 | 2 803.9±518.1$^d$ | 8 186.6±3 987.9$^d$ | 8 265.3±4 092.0$^d$ | 3 211.9±1 151.7$^d$ | 2 161.3±814.6 |

HR: heart rate, BT: body temperature, Amy: amylase. Group 1: controls; group 2: low-volume continuous veno-venous hemofiltration (CVVH) (20 mL/kg body weight [BW]/h); group 3: high-volume CVVH (100 mL/kg BW); NC, not calculated (no survival). $^a$$P$<0.05 and $^b$$P$<0.01 *vs* the respective value in controls; $^c$$P$<0.05 and $^d$$P$<0.01 *vs* baseline values, respectively.

**Table 2** Hemodynamic parameters (mean±SD)

| Parameter | Group | Baseline | 6 h | 12 h | 24 h | 36 h | 48 h |
|---|---|---|---|---|---|---|---|
| MAP (mmHg) | 1 | 126.5±7.76 | 95.5±10.20$^{d}$ | 87.38±12.45$^{d}$ | 81.83±5.08$^{d}$ | 80.0±10.0$^{d}$ | NC |
| | 2 | 126.3±7.19 | 95.6±7.44$^{d}$ | 104.5±6.82$^{ad}$ | 102.0±10.64$^{ad}$ | 100.8±9.74$^{ac}$ | 84.5±13.44 |
| | 3 | 123.3±4.43 | 117.8±9.07$^{ac}$ | 116.3±7.80$^{a}$ | 106.8±9.79$^{ad}$ | 104.5±6.74$^{ad}$ | 99.57±11.97 |
| MPAP (mmHg) | 1 | 24.5±1.51 | 25.0±1.07 | 26.8±1.16$^{d}$ | 30.0±2.76$^{d}$ | 27.3±3.06 | NC |
| | 2 | 24.3±2.25 | 26.1±2.59 | 26.4±2.33 | 28.4±3.58$^{c}$ | 29.5±2.38 | 29.0±8.49 |
| | 3 | 24.4±1.85 | 25.9±1.25 | 22.1±1.81$^{a}$ | 25.4±2.92$^{a}$ | 27.3±3.58$^{c}$ | 27.4±1.72 |
| PCWP (mmHg) | 1 | 10.1±1.96 | 9.1±2.85 | 10.8±1.98 | 14.2±3.19$^{c}$ | 11.0±2.65 | NC |
| | 2 | 10.5±1.60 | 9.0±4.14 | 11.5±3.25 | 11.8±4.17 | 11.5±7.14 | 8.5±4.95 |
| | 3 | 10.3±0.71 | 8.8±1.98 | 9.6±1.60 | 10.3±2.87$^{a}$ | 10.0±3.82 | 14.0±3.00 |
| CVP (mmHg) | 1 | 8.6±2.07 | 7.3±2.12 | 5.5±2.07$^{c}$ | 9.2±3.92 | 9.0±1.73 | NC |
| | 2 | 8.0±2.14 | 8.6±4.41 | 7.6±3.85 | 8.6±2.50 | 11.5±6.24 | 7.0±5.66 |
| | 3 | 7.9±1.36 | 6.5±1.93 | 6.9±1.36 | 7.3±1.98 | 7.4±2.07 | 8.3±2.21 |
| CI (L/min/m$^{2}$) | 1 | 4.5±0.55 | 6.2±0.64$^{d}$ | 5.9±1.19$^{c}$ | 3.1±0.41$^{d}$ | 2.4±0.70 | NC |
| | 2 | 4.7±0.75 | 5.4±0.90$^{c}$ | 5.9±0.86$^{c}$ | 5.1±1.79$^{a}$ | 4.6±2.43 | 3.7±0.12 |
| | 3 | 4.6±0.54 | 5.0±0.97$^{a}$ | 4.2±0.73$^{a}$ | 4.8±0.56$^{a}$ | 5.3±1.10$^{a}$ | 6.3±1.17 |
| SVR (dyn•s•cm$^{-5}$) | 1 | 2 130.2±204.5 | 1 176.8±253.9$^{d}$ | 1 465.0±788.3$^{c}$ | 1 915.8±397.8 | 3 617.7±374.1$^{d}$ | NC |
| | 2 | 2 061.2±407.1 | 1 329.6±354.8$^{d}$ | 1 349.9±218.6$^{d}$ | 1 573.0±633.1 | 1 988.1±942.4a | 1 674.2±463.6 |
| | 3 | 2 034.4±315.6 | 1 820.8±380.3$^{a}$ | 2 172.3±371.7$^{a}$ | 1 664.6±268.1 | 1 512.6±321.6$^{a}$ | 1 187.4±201.4 |

MAP: mean arterial pressure, MPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CVP: central venous pressure, CI: cardiac index, SVR: systemic vascular resistance. Group 1: controls; group 2: low-volume continuous veno-venous hemofiltration (CVVH) (20 mL/kg body weight [BW]/h); group 3: high-volume CVVH (100 mL/kg BW); NC, not calculated (no survival). $^{a}P<0.05$ and $^{b}P<0.01$ *vs* the respective value in controls; $^{c}P<0.05$ and $^{d}P<0.01$ *vs* baseline values, respectively.

**Table 3** Oxygen metabolism parameters (mean±SD)

| Parameter | Group | Baseline | 6 h | 12 h | 24 h | 36 h | 48 h |
|---|---|---|---|---|---|---|---|
| $DO_2$ | 1 | 774.1±142.9 | 1 044.5±154.2$^{d}$ | 1 029.4±307.6 | 501.3±75.0$^{d}$ | 389.4±178.8 | NC |
| | 2 | 751.4±206.0 | 811.6±197.4$^{a}$ | 840.6±195.7 | 673.6±189.8 | 458.4±166.8$^{c}$ | 320.9±71.8 |
| | 3 | 674.2±76.7 | 706.5±95.4$^{a}$ | 552.1±119.7$^{a}$ | 489.5±71.8$^{bd}$ | 474.9±63.0$^{d}$ | 517.2±163.7 |
| $VO_2$ | 1 | 215.3±44.9 | 336.6±103.1$^{d}$ | 331.4±153.2 | 140.0±46.4$^{d}$ | 108.0±55.1$^{c}$ | NC |
| | 2 | 224.4±67.0 | 365.9±136.4$^{d}$ | 331.0±70.0$^{d}$ | 293.1±105.4$^{a}$ | 200.6±133.8 | 93.7±41.9 |
| | 3 | 203.7±61.1 | 366.1±52.6$^{d}$ | 247.8±73.7$^{b}$ | 178.5±44.0$^{b}$ | 163.2±45.1 | 167.8±90.0 |
| OER | 1 | 27.8±2.0 | 31.7±7.7 | 31.5±6.7 | 27.6±7.2 | 27.6±3.1 | NC |
| | 2 | 29.9±4.6 | 44.0±9.0$^{ad}$ | 40.0±5.8$^{ac}$ | 43.5±10.4$^{ac}$ | 41.0±12.9 | 28.5±6.7 |
| | 3 | 30.0±6.8 | 51.9±3.2$^{ad}$ | 44.6±7.3$^{ad}$ | 36.3±7.2$^{ad}$ | 33.9±6.4 | 31.0±7.8 |

$DO_2$: oxygen delivery, $VO_2$: oxygen consumption, OER: oxygen extraction ratio. Group 1: controls; group 2: low-volume continuous veno-venous hemofiltration (CVVH) (20 mL/kg body weight [BW]/h); group 3: high-volume CVVH (100 mL/kg BW); NC, not calculated (no survival). $^{a}P<0.05$ and $^{b}P<0.01$ *vs* the respective value in controls; $^{c}P<0.05$ and $^{d}P<0.01$ *vs* baseline values, respectively.

higher in the control group compared to the treatment groups after the induction of pancreatitis (Table 3). In contrast, no differences in $VO_2$ were observed between the CVVH groups and control group (Table 3). As a result, OER was found to be significantly higher in animals undergoing CVVH.

### *Biochemical measurements*

The activities of amylase in blood serum ranged from 115 to 543 U/L before the induction of pancreatitis. Pancreatitis resulted in a significant rise in amylase activities in all groups. Slight differences between groups did not reach statistical significance (Table 1).

## DISCUSSION

Continuous hemofiltration, especially continuous venovenous hemofiltration (CVVH), was developed as a continuous renal replacement therapy (CRRT) for patients with severe conditions and has been widely performed in critical care[19]. In the present study we investigated the potential use of prophylactic CVVH to attenuate pancreatitis-induced SIRS and MODS. There was a significant effect on several organ functions, most notably on the cardiovascular system.

A hyperdynamic hemodynamic state may exist in the early stages of moderate and severe pancreatitis and myocardial depression may be evident in severe pancreatitis, as could be observed in all animals in the early phase of pancreatitis. This cardiovascular reaction, which could also be observed in patients with severe infectious SIRS[20], seems to be necessary to maintain oxidative metabolism and cellular integrity, since patients who fail to increase their CO spontaneously, despite volume loading, are known to have a comparably poor prognosis[21]. Nevertheless, although elevated CO is usually accompanied with an increased $DO_2$ (provided hemoglobin concentrations and oxygen saturation are unchanged), this might still be insufficient to meet the metabolic demand of peripheral tissues, because of increased oxygen demand and/or microcirculatory mismatching[2,21]. The latter factors, which contribute to tissue hypoxia, might be aggravated by directly impaired oxygen utilization due to a decreased mitochondrial redox state induced, for example, by cytokines or activated complement factors[2,4]. Hence, OER is usually reduced in critically ill patients with a hyperdynamic circulatory state and there still might be a hidden oxygen debt in spite of increased $DO_2$[2,21-23].

It is thus proposed to increase $DO_2$ further with inotropics, e.g., dobutamine, to meet the oxygen demand in patients with severe SIRS[24]. However, in contrast with encouraging early reports, to date there is little evidence that patients suffering from hyperdynamic circulatory failure benefit from increasing CO pharmacologically[22-24]. This treatment modality increases the workload of the heart and might lead to increased non-oxidative oxygen metabolism and decreased oxygen extraction rate in some patients, e.g., those with limited cardiovascular reverse[22]. Thus, enhancing oxygen extraction may represent an alternative therapeutic approach which is more appropriate for the underlying pathophysiology. Alternatively, CVVH may directly decrease CO, which is compensated for by an increase in OER. In any case, as a net effect, CVVH significantly increases oxygen extraction without reducing $VO_2$ while the post-SIRS increase of CI and $DO_2$ is attenuated, although not prevented.

The mechanisms contributing to the attenuation of the hyperdynamic state remain speculative and may involve simple cooling effects[25,26] (as observed in the early course of CVVH, i.e., at hours 6 and 12 of the present study) or removal of filterable cardiodepressant mediators or factors involved in impaired microcirculation or cellular oxygen utilization[13,15,16]. In support of the latter concept, there is at least correlative evidence that an increase in MAP and SVR in septic animals after onset of CVVH is paralleled by a decrease in the circulating anaphylatoxins C3a and C5a[27] known to impair cellular oxygen uptake[4]. For several years, the issue of the ability of hemofiltration to remove inflammatory mediators has remained controversial. Numerous *ex vivo* as well as animal and human studies[28] have shown that synthetic filters commonly used in hemofiltration can extract nearly every substance involved in sepsis to a certain degree. More studies are expected to investigate whether CVVH attenuates the impaired cellular metabolism in patients with SIRS. Nevertheless, despite the significant clearance of some of these mediators, plasma concentrations of these mediators might not be necessarily lower, indicating increased production due to CVVH[28,29]. Thus alternative mechanisms, such as simple cooling or a combination of physical factors with removal of vasoactive factors may mediate the observed attenuation of the hyperdynamic circulation.

Oxygen consumption was not directly measured but calculated according to the Fick principle in the present study, which may lead to mathematical coupling of $VO_2$ and $DO_2$ reflecting a possible methodological problem[30]. However, if a decreased $DO_2$ is measured (as in the present study for the CVVH groups), mathematical coupling would result in an erroneously lower $VO_2$. In contrast, in the present study there was no significant decrease in $VO_2$ in animals subjected to CVVH, despite a significantly lower $DO_2$ than in controls. Although we have to concede that measuring $VO_2$ directly is preferable, mathematical coupling would even underestimate the beneficial effect of CVVH on oxygen extraction observed in the present study.

The attenuation of hyperdynamic cardiocirculatory response in animals subjected to prophylactic CVVH may, as discussed above, in part result from their lower BT due to heat loss through the extracorporeal circuit. However, the difference in CI, SVR and $DO_2$ between the two CVVH groups, when differences in BT could not be detected, would suggest the contribution of factors other than simple cooling, e.g., removal of humoral factors mediating the hyperdynamic response. Furthermore, if a decrease in BT would be the main factor attenuating the hyperdynamic response to SIRS, a decrease in $VO_2$ in patients subjected to CVVH would be expected[26], but this was not the case.

In conclusion, our data indicate that the hyperdynamic circulatory response to severe acute pancreatitis can be attenuated by CVVH, especially high-volume CVVH. In contrast, there are no significant changes in $VO_2$ related to the prophylactic use of CVVH. Thus, oxygen extraction may be improved in pancreatitis pigs by CVVH.

## REFERENCES


1 **Beger HG**, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. *World J Surg* 1997; **21**: 130-135

2 **Beal AL,** Cerra FB. Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction. *JAMA* 1994; **271**: 226-233

3 **Mayer J**, Rau B, Gansauge F, Beger HG. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut* 2000; **47**: 546-552

4 **Mohr M**, Hopken U, Oppermann M, Mathes C, Goldmann K, Siever S, Gotze O, Burchardi H. Effects of anti-C5a monoclonal antibodies on oxygen use in a porcine model of severe sepsis. *Eur J Clin Invest* 1998; **28**: 227-234

5 **Reinhart K,** Wiegand-Lohnert C, Grimminger F, Kaul M, Withington S, Treacher D, Eckart J, Willatts S, Bouza C, Krausch D, Stockenhuber F, Eiselstein J, Daum L, Kempeni J. Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. *Crit Care Med* 1996; **24**: 733-742

6 **Fisher CJ,** Slotman GJ, Opal SM, Pribble JP, Bone RC, Emmanuel G, Ng D, Bloedow DC, Catalano MA. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* 1994; **22**: 12-21

7 **Kamijo Y,** Soma K, Sugimoto K, Tsuruta H, Ohwada T. The effect of a hemofilter during extracorporeal circulation on hemodynamics in patients with SIRS. *Intensive Care Med* 2000; **26**: 1355-1359

8 **Suffredini AF**. Current prospects for the treatment of clinical sepsis. *Crit Care Med* 1994; **22**: S12-S18

9 **Lin E,** Lowry SF. Inflammatory cytokines in major surgery: a functional perspective. *Intensive Care Med* 1999; **25**: 255-257

10 **Echtenacher B,** Falk W, Mannel DN, Krammer PH. Requirement of endogenous tumor necrosis factor/cachectin for recovery from experimental peritonitis. *J Immunol* 1990; **145**: 3762-3766

11 **Ziegenfuss T,** Wanner GA, Grass C, Bauer I, Schuder G, Kleinschmidt S, Menger MD, Bauer M. Mixed agonistic-antagonistic cytokine response in whole blood from patients undergoing abdominal aortic aneurysm repair. *Intensive Care Med* 1999; **25**: 279-287

12 **Bone RC**. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 1996; **24**: 1125-1128

13 **van Bommel EF**. Should continuous renal replacement therapy be used for 'non-renal' indications in critically ill patients with shock? *Resuscitation* 1997; **33**: 257-270

14 **Bellomo R**. Continuous hemofiltration as blood purification in sepsis. *New Horiz* 1995; **3**: 732-737

15 **Grootendorst AF,** van Bommel EF, van der Hoven B, van Leengoed LA, van Osta AL. High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. *Intensive Care Med* 1992; **18:** 235-240

16 **Heering P,** Morgera S, Schmitz FJ, Schmitz G, Willers R, Schultheiss HP, Strauer BE, Grabensee B. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. *Intensive Care Med* 1997;

**23**: 288-296
17 **Koperna T,** Vogl SE, Poschl GP, Hamilton G, Roder G, Germann P. Cytokine patterns in patients who undergo hemofiltration for treatment of multiple organ failure. *World J Surg* 1998; **22**: 443-447; discussion 448
18 **Tu WF,** Zhu WM, Li JS. Setting-up of the experimental model of severe acute pancreatitis in pigs. *Jinling Yiyuan Xuebao* 1997; **10:** 235-237
19 **Wang H,** Li WQ, Zhou W, Li N, Li JS. Clinical effects of continuous high volume hemofiltration on severe acute pancreatitis complicated with multiple organ dysfunction syndrome. *World J Gastroenterol* 2003; **9**: 2096-2099
20 **Mitsuo T,** Shimazaki S, Matsuda H. Right ventricular dysfunction in septic patients. *Crit Care Med* 1992; **20**: 630-634
21 **Hayes MA,** Timmins AC, Yau EH, Palazzo M, Watson D, Hinds CJ. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med* 1997; **25**: 926-936
22 **Yu M,** Burchell S, Hasaniya NW, Takanishi DM, Myers SA, Takiguchi SA. Relationship of mortality to increasing oxygen delivery in patients > or = 50 years of age: a prospective, randomized trial. *Crit Care Med* 1998; **26**: 1011-1019
23 **Haupt MT.** Impaired oxygen extraction in sepsis: is supranormal oxygen delivery helpful? *Crit Care Med* 1997; **25**: 904-905
24 **Fleming A,** Bishop M, Shoemaker W, Appel P, Sufficool W, Kuvhenguwha A, Kennedy F, Wo CJ. Prospective trial of supranormal values as goals of resuscitation in severe trauma. *Arch Surg* 1992; **127**: 1175-1179; discussion 1179-1181
25 **Yagi N,** Leblanc M, Sakai K, Wright EJ, Paganini EP. Cooling effect of continuous renal replacement therapy in critically ill patients. *Am J Kidney Dis* 1998; **32**: 1023-1030
26 **Matamis D,** Tsagourias M, Koletsos K, Riggos D, Mavromatidis K, Sombolos K, Bursztein S. Influence of continuous haemofiltration-related hypothermia on haemodynamic variables and gas exchange in septic patients. *Intensive Care Med* 1994; **20**: 431-436
27 **Hoffmann JN,** Hartl WH, Deppisch R, Faist E, Jochum M, Inthorn D. Effect of hemofiltration on hemodynamics and systemic concentrations of anaphylatoxins and cytokines in human sepsis. *Intensive Care Med* 1996; **22**: 1360-1367
28 **De Vriese AS,** Vanholder RC, Pascual M, Lameire NH, Colardyn FA. Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies? *Intensive Care Med* 1999; **25:** 903-910
29 **Sander A,** Armbruster W, Sander B, Daul AE, Lange R, Peters J. Hemofiltration increases IL-6 clearance in early systemic inflammatory response syndrome but does not alter IL-6 and TNF alpha plasma concentrations. *Intensive Care Med* 1997; **23**: 878-884
30 **Hanique G,** Dugernier T, Laterre PF, Dougnac A, Roeseler J, Reynaert MS. Significance of pathologic oxygen supply dependency in critically ill patients: comparison between measured and calculated methods. *Intensive Care Med* 1994; **20**: 12-18

**Edited by** Wang XL **Proofread by** Zhu LH