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

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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] or removing[6] 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[7]. Although anti-mediator strategies are successful in experimental models of endotoxia, 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[8,9]. 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[10].

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[11,12]. 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[13,14]. 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), intraduodenal infusion of sodium taurocololate [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), cardiac index (CI), oxygen delivery (DO2), oxygen consumption (VO2) and oxygen extraction ratio (OER) were calculated from CO, CaO2 and CVO2 according to the following equations: DO2 [mL/(min·m2)] = CI[(l/(min·m2))] × [CaO2(mL/100mL) × 10], VO2 = CI[(l/(min·m2))] × [CV02(mL/100mL) × 10], and OER = VO2/DO2.

**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 Scheffé 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=0.01 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, Table 2). 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 °C 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, DO2 was found to be significantly

| Parameter | Group | Baseline | 6 h | 12 h | 24 h | 36 h | 48 h |
|-----------|-------|----------|-----|------|------|------|------|
| HR (bpm)  | 1     | 123±8.2  | 179±9.7  | 194±20.8  | 164±26.2 | 132±23.0 | NC  |
|           | 2     | 123±8.2  | 159±10.4  | 165±15.5  | 159±21.6  | 139±25.2 | 141±36.1 |
|           | 3     | 123±8.3  | 149±9.4  | 155±23.8  | 148±21.4  | 148±17.6  | 138±18.4 |
| BT (°C)   | 1     | 37.1±1.2  | 39.6±1.1  | 40.0±0.9  | 36.0±0.6  | 35.6±0.6  | NC  |
|           | 2     | 37.9±0.7  | 38.7±1.2  | 38.7±0.6  | 36.8±1.2  | 36.1±1.3  | 37.5±3.4  |
|           | 3     | 37.8±0.5  | 38.3±0.6  | 38.6±0.8  | 38.8±0.8  | 38.5±0.2  | 39.0±0.3  |
| Amy (U/I) | 1     | 238±122.6  | 3 635±427.2  | 9 535±8 502.6  | 7 535±7 576.3  | 5 502±7 976.8  | NC  |
|           | 2     | 336±123.8  | 3 309±1331.2  | 8 199±5 881.0  | 8 441±5 730.4  | 2 960±5 292.6  | 3 168±3 136.3  |
|           | 3     | 237±66.7  | 2 803±518.1  | 8 186±3 987.9  | 8 265±3 092.0  | 3 211±9 151.7  | 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). *P<0.05 and **P<0.01 vs the respective value in controls; †P<0.05 and ‡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 VO₂ 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[9]. 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 phase of pancreatitis, which could also be observed in peripheral tissues, because of increased oxygen demand and might still be insufficient to meet the metabolic demand of central organs. This could be observed in the cardiovascular reaction, which could also be observed in depression may be evident in severe pancreatitis, as could be observed in the respective value in controls; P<0.05 and P<0.01 vs the respective value in controls; P<0.05 and P<0.01 vs baseline values, respectively.

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).

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<sup>a</sup> | 87.38±12.45<sup>a</sup> | 81.83±5.08<sup>a</sup> | 80.0±10.0<sup>a</sup> | NC   |
|                 | 2     | 126.3±7.19 | 95.6±7.44<sup>a</sup> | 104.5±6.82<sup>ad</sup> | 102.0±10.64<sup>ad</sup> | 100.8±9.74<sup>ac</sup> | 84.5±13.44 |
|                 | 3     | 123.3±4.43 | 117.8±7.07<sup>ac</sup> | 116.3±7.80<sup>ac</sup> | 106.8±9.79<sup>ad</sup> | 104.5±5.74<sup>ad</sup> | 99.5±11.97 |
| MPAP (mmHg)     | 1     | 24.5±1.51  | 25.0±1.07 | 26.8±1.16<sup>ad</sup> | 30.0±2.76<sup>ad</sup> | 27.3±3.06<sup>ac</sup> | NC |
|                 | 2     | 24.3±2.25  | 26.1±2.59 | 26.4±2.33 | 28.4±3.58<sup>ac</sup> | 29.5±2.38 | 29.0±8.49 |
|                 | 3     | 24.4±1.85  | 25.9±1.25 | 22.1±1.81<sup>ad</sup> | 25.4±2.92<sup>ad</sup> | 27.3±5.38<sup>ad</sup> | 27.4±1.72 |
| PCWP (mmHg)     | 1     | 10.1±1.96  | 9.1±2.85  | 10.8±1.98 | 14.2±3.19 | 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<sup>ad</sup> | 10.0±3.82 | 14.0±3.00 |
| CVP (mmHg)      | 1     | 1.86±0.27  | 7.3±2.12  | 5.5±2.07<sup>c</sup> | 9.2±3.92 | 9.0±1.73 | NC   |
|                 | 2     | 8.0±2.14   | 8.6±4.44  | 7.6±3.85  | 8.6±2.50 | 11.5±6.24 | 7.0±6.66 |
|                 | 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/m²)   | 1     | 4.5±0.55   | 6.2±0.64<sup>d</sup> | 5.9±1.19<sup>c</sup> | 3.1±0.41<sup>d</sup> | 2.4±0.70 | NC   |
|                 | 2     | 4.7±0.75   | 5.4±0.90<sup>d</sup> | 5.9±0.86<sup>c</sup> | 5.1±1.79<sup>c</sup> | 4.6±2.43 | 3.7±0.12 |
|                 | 3     | 4.6±0.54   | 5.0±0.97<sup>d</sup> | 4.2±0.73<sup>ad</sup> | 4.8±0.56<sup>ad</sup> | 5.3±1.10<sup>a</sup> | 6.3±1.17 |
| SVR (dyn*s*cm⁻³) | 1     | 2 130.2±204.5 | 1 176.8±253.9<sup>a</sup> | 1 465.0±788.3<sup>c</sup> | 1 915.8±397.8<sup>c</sup> | 3 617.7±374.1<sup>c</sup> | NC |
|                 | 2     | 2 061.2±407.1 | 1 329.6±354.8<sup>a</sup> | 1 349.9±218.6<sup>d</sup> | 1 573.0±633.1<sup>d</sup> | 1 988.1±942.4<sup>a</sup> | 1 674.2±463.6 |
|                 | 3     | 2 034.4±315.6 | 1 820.8±380.3<sup>a</sup> | 2 172.3±571.7<sup>a</sup> | 1 664.6±268.1 | 1 512.6±321.6<sup>a</sup> | 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).<sup>a</sup>P<0.05 and <sup>b</sup>P<0.01 vs the respective value in controls; <sup>c</sup>P<0.05 and <sup>d</sup>P<0.01 vs baseline values, respectively.
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[24]. 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 DO₂[2,21-23].

It is thus proposed to increase DO₂ 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-oxygenate oxygen metabolism and decreased oxygen extraction rate in some patients, e.g., those with limited cardiovascular reserve[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 VO₂ while the post-SIRS increase of CI and DO₂ 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 is paralleled by a decrease in the circulating concentrations of these mediators might not be necessarily decreased, indicating increased production due to CVVH[27].

In the present study, the relationship between CVVH and VO₂ was measured (as in the present study for the CVVH groups), mathematical coupling would result in an erroneously lower VO₂. In contrast, in the present study there was no significant decrease in VO₂ in animals subjected to CVVH, despite a significantly lower DO₂ than in controls. Although we have to concede that measuring VO₂ 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 DO₂ 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 VO₂ in patients subjected to CVVH would be expected[20], 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 VO₂ related to the prophylactic use of CVVH. Thus, oxygen extraction may be improved in pancreatitis pigs by CVVH.

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