Original Article

Effects of continuous venovenous haemofiltration-induced cooling on global haemodynamics, splanchnic oxygen and energy balance in critically ill patients

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Abstract

Background. A number of haemodialysis studies have demonstrated beneficial effects of cooler dialysates on global haemodynamics in chronic dialysis patients. However, the effects of continuous venovenous haemofiltration (CVVH)-induced cooling on regional perfusion and energy metabolism in critically ill septic patients have not been well defined.

Methods. Nine septic mechanically ventilated patients (age 40–69 years) were investigated during CVVH (ultrafiltration 30–35 ml/kg/h). Baseline data (=WARM 1) were collected when core temperature (Tc) was >37.5°C; the second data set (=COLD) was obtained after 120 min of ‘cooling’; and a third set (=WARM 2) was obtained after 120 min of ‘rewarming’. During ‘warming’ (WARM 1 and 2, respectively), both substitution fluids (SFs) and ‘returned’ blood (RB) were warmed (37°C), whereas during ‘cooling’, the SFs were at 20°C and RB was not warmed. We measured hepatic venous (HV) haemoglobin oxygen saturation (ShvO2), blood gases, lactate and pyruvate. Gastric mucosal PCO2 (PgmCO2) was measured by air tonometry and the gastric mucosal – arterial PCO2 difference (PCO2 gap) was calculated. Haemodynamic monitoring was performed with arterial and pulmonary arterial thermodilution catheters.

Results. Tcs were significantly altered [WARM 1, 37.9°C (37.6, 38.3); COLD, 36.8°C (36.3, 37.1); WARM 2, 37.5°C (37.0, 38.0); P<0.001; data are median, 25th and 75th percentiles, respectively]. Systemic vascular resistance significantly increased during cooling. As a result, mean arterial pressure increased. Cooling was associated with significant decreases in heart rate, cardiac output, systemic oxygen delivery and consumption. ShvO2 did not change [WARM 1, 51.0% (44.0, 59.5); COLD, 49.0% (42.0, 58.0); WARM 2, 51.0% (46.0, 57.0); P=NS]. The splanchnic oxygen extraction ratio, the HV lactate to pyruvate ratio, HV acid base status and PCO2 gap remained unchanged.

Conclusion. Mild core cooling induced by CVVH may not affect hepatosplanchnic oxygen and energy balance in septic critically ill patients, even though it affects global haemodynamics.

Keywords: continuous renal replacement therapy; cooling; critically ill; hepatosplanchnic region; hypothermia; sepsis

Introduction

A number of studies have investigated the impact of variations in dialysate temperature on central haemodynamics during intermittent haemodialysis (IHD) in chronic dialysis patients [1–4]. Most groups have used the rise in mean arterial pressure (MAP) as a surrogate for improvement in global haemodynamics during IHD. These studies consistently showed that MAP increased when cooler dialysates were used (usually 35°C) compared with use of standard dialysate temperatures (37°C) [1–5]. This beneficial haemodynamic effect was thought to be secondary to increased peripheral vascular tone and venous reactivity [3,4]. However, van der Sande et al. [5] recently pointed out that both absolute changes in core temperature (Tc) and a negative energy transfer may be important for vascular changes in this setting.

During the last decade, continuous renal replacement therapies (CRRTs) have been used increasingly in
critically ill patients with acute renal failure. A number of studies have investigated cytokine elimination during CRRT [6]. Interestingly, de Vries et al. [7] showed that haemodynamic responses during continuous venovenous haemofiltration (CVVH) may not be related to changes in plasma cytokine levels [7]. In contrast, only a few studies have systematically investigated temperature changes during CRRT and evaluated their relationship to haemodynamics [8–10]. In one of these studies, marked hypothermia induced by CRRT led in some patients to shivering, profound peripheral vasoconstriction and immune system dysfunction [8]. Therefore, current practice for CRRT is to warm up substitution fluids (SFs) and/or dialysate fluids, the ‘returned blood’ (RB) or both to avoid significant hypothermia. Thus far, the optimal Tc target remains unknown, particularly in septic patients. Several studies have documented an increased MAP when mild core cooling (MCC) was achieved during CRRT [9,10].

However, it remains to be determined whether the beneficial effect of cooling on MAP may be outweighed by potential negative effects on tissue perfusion, such as in the hepatosplanchnic region (HSR) [11]. Given the postulated role of the HSR in the pathophysiology of sepsis and multiple organ dysfunction syndrome, this type of effect may be of great importance in critically ill patients [12]. We therefore performed a prospective clinical study to test the effects of CVVH-induced MCC on hepatosplanchnic oxygen kinetics, energy balance and whole body haemodynamics in critically ill septic patients.

**Subjects and methods**

This study was approved by the local University Hospital Ethics Committee, and written informed consent was obtained from next of kin. It was conducted according to the principles established in the Helsinki Declaration.

**Study cohort**

We studied nine patients (male/female, 7/2) that met the following criteria: (i) severe sepsis or septic shock [13]; (ii) acute renal dysfunction requiring CRRT (see below); (iii) Tc before CVVH >38°C; and (iv) age between 18 and 75 years. Patients were required to have at least one of the following criteria for CVVH initiation: serum creatinine level >180 μmol/l or serum creatinine increase >40 μmol/24 h, or urine output <400 ml/12 h despite adequate fluid resuscitation and diuretic administration.

The exclusion criteria were: (i) significant haemodynamic instability defined as the need for norepinephrine dose change during the 4 h before the study; (ii) a cardiac index <2.51/min/m²; or (iii) any contra-indication for hepatic venous catheterization as well as for gastric tonometry tube placement.

The patient characteristics are shown in Table 1. All patients were mechanically ventilated (volume control mode, tidal volume 8–10 cm H₂O/kg, positive end expiratory pressure 10–14 cm H₂O, no changes in ventilator setting during the study) and sedated with midazolam and fentanyl infused at a constant rate in order to avoid stress- and/or shivering-induced changes in sympathetic tone and metabolic rate. Before the study, adequate fluid resuscitation was ensured by monitoring filling pressures, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). Norepinephrine was titrated to maintain MAP >70 mmHg as needed. During the study period, fluid infusion rates were kept at a constant level, blood transfusions were not given, and no other therapeutic interventions or nursing procedures were performed.

**Procedures, measurements and calculations**

Routine invasive haemodynamic monitoring included use of arterial and pulmonary arterial (PA) thermodilution catheters. An angiography catheter (5 Fr, MPA 2, Cordis Corp, Miami, FL) was placed via the right jugular vein into a hepatic vein under ultrasound guidance [14].

Tc was measured with a thermistor from the PA catheter, and peripheral temperature (Tp) was monitored using a termistor attached to the skin in the toe area. Arterial, mixed venous and hepatic venous blood gases as well as haemoglobin oxygen (O₂) saturation were measured by co-oximetry (ABL 520 and OSM-3, Radiometer, Copenhagen, Denmark). For better accuracy, hepatic venous blood was sampled in duplicate at 5 min intervals at the end of each study period, and the mean of these two samples was the final value. The mean coefficient of variation between these two

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Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>APACHE II&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SOFA&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Tc&lt;sup&gt;c&lt;/sup&gt; (°C)</th>
<th>Urine output&lt;sup&gt;d&lt;/sup&gt; (ml/h)</th>
<th>Urea&lt;sup&gt;e&lt;/sup&gt; (mmol/l)</th>
<th>Creatinine&lt;sup&gt;e&lt;/sup&gt; (μmol/l)</th>
<th>ICU day&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CVVH (h)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>NE&lt;sup&gt;e&lt;/sup&gt; (μg/kg/min)</th>
<th>Hospital survival&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>40</td>
<td>85</td>
<td>18/10</td>
<td>39</td>
<td>20</td>
<td>29</td>
<td>380</td>
<td>5</td>
<td>20</td>
<td>0.04</td>
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<td>Pneumonia</td>
<td>69</td>
<td>98</td>
<td>24/9</td>
<td>39</td>
<td>9</td>
<td>13</td>
<td>403</td>
<td>6</td>
<td>8</td>
<td>0.03</td>
<td>1</td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>48</td>
<td>50</td>
<td>18/12</td>
<td>40</td>
<td>100</td>
<td>28</td>
<td>320</td>
<td>3</td>
<td>18</td>
<td>0.53</td>
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<tr>
<td>Pneumonia</td>
<td>47</td>
<td>70</td>
<td>14/16</td>
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<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>52</td>
<td>70</td>
<td>24/12</td>
<td>38</td>
<td>0</td>
<td>27</td>
<td>260</td>
<td>6</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>48</td>
<td>85</td>
<td>28/11</td>
<td>38.5</td>
<td>40</td>
<td>29</td>
<td>550</td>
<td>3</td>
<td>8</td>
<td>0.02</td>
<td>1</td>
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<tr>
<td>Pneumonia</td>
<td>47</td>
<td>75</td>
<td>20/11</td>
<td>38.5</td>
<td>0</td>
<td>34</td>
<td>399</td>
<td>3</td>
<td>8</td>
<td>0.06</td>
<td>1</td>
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</tr>
<tr>
<td>Pneumonia</td>
<td>61</td>
<td>92</td>
<td>27/11</td>
<td>38.6</td>
<td>50</td>
<td>33</td>
<td>496</td>
<td>7</td>
<td>24</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure assessment; ICU, intensive care unit; Tc, core temperature; CVVH, continuous venovenous haemofiltration; NE, norepinephrine
<sup>a</sup>Admission day; <sup>b</sup>at study day; <sup>c</sup>before CVVH; <sup>d</sup>time between CVVH start and study; <sup>e</sup>1 = survivor, 0 = non-survivor.
measurements was 2.1 ± 2.0%. Arterial and hepatic venous blood used for analysis of lactate and pyruvate was immediately deproteinized in cold perchloric acid, and lactate and pyruvate concentrations were measured enzymatically and analysed spectrophotometrically (Hitachi 717, Boehringer Mannheim, Germany). We subsequently calculated the hepatic venous lactate to pyruvate (L/p) ratio as a surrogate for cytosolic redox state in the HSR [15].

During the entire experiment, oxygen consumption (VO2), carbon dioxide production (VCO2) and resting energy expenditure (REE) were measured continuously by indirect calorimetry (DELTATRAC, Datex, Instrumentarium Corp., Helsinki, Finland). The mean of five consecutive 1-min measurements at the end of each period was used for analysis. The VO2 measurement was invalid in one patient due to a high fraction of inspired oxygen (>80%). The systemic oxygen delivery (DO2syst) was determined from a standard formula. The systemic oxygen extraction ratio (syst O2ER) was calculated as the ratio of arterial to mixed venous O2 content difference over arterial O2 content. Splanchnic oxygen extraction (spl O2ER) was assessed as the ratio of the arterial – hepatic venous O2 content difference to arterial O2 content.

Gastric mucosal PCO2 (PgmCO2) was measured semi-continuously (time equilibration 10 min) by automated air tonometry (Tonocap, Datex-Ohmeda, Helsinki, Finland) [16]. For the final analysis, PgmCO2 was averaged from the last two consecutive values from each measurement period, and the gastric mucosal to arterial PCO2 difference (PCO2 gap) was then calculated.

Each patient was given the proton pump inhibitor omeprazol (120 mg/day i.v.) in order to increase gastric juice pH above 4, which may improve the accuracy of the PgmCO2 measurement.

CVVH setting (Figure 1)
CVVH was performed using a HYGIEIA PLUS (Unbridge, Middlesex, UK) machine having a polysulfone haemofilter (Ultraflux AV 600S, 1.4 m2, Germany) that was not changed before or during the study. Blood flow was 150 ± 15 ml/min. SF (lactate-buffered in six patients, bicarbonate-buffered in three patients) was given in pre-filter post-blood pump mode. The net fluid removal was 0–200 ml/h according to haemodynamic status and was not changed during the study. Total ultrafiltration rate was 30–35 ml/kg/h. Anticoagulation was achieved using unfractionated heparin (lactate-buffered SF) or 2.2% sodium citrate (bicarbonate-buffered SF). The rates of SF and anticoagulation were kept constant for at least 8 h before and during the study period.

Protocol (Figure 1)
Baseline data (=WARM 1) were collected when both SF and RB were warmed to 37°C in order to achieve Tc > 37.5°C, and this temperature was maintained for a minimum of 3 h. SF were warmed to 37°C using a heating device incorporated in the HYGIEIA PLUS machine, and RB (i.e. the line connecting the end of the haemofilter and double lumen catheter) was warmed to 37°C by a countercurrent heating device HOT-LINE (Level 1 Technologies Inc., Rockland, MA). The second data set (=COLD) was obtained after 120 min of ‘cooling down’ (SF 20°C with temperature control by an in-house temperature sensor; RB without warming), and the third data set (=WARM 2) was obtained after 120 min of ‘rewarming’ (the same setting as during WARM 1). The room temperature was 24–26°C.

Statistical analysis
All values shown are medians, as well as 25th and 75th percentiles. After the exclusion of normal distribution, differences between periods were analysed by the Friedman rank sign analysis of variance and subsequent Dunn’s tests for multiple comparisons when appropriate. Statistical significance was set at $P < 0.05$. Linear correlations were tested using the Spearman’s rank order method.

Results
During the study, all patients remained haemodynamically stable and the doses of norepinephrine, when needed, were kept constant (Table 1). No patient had shivering during the study and muscle relaxants were...
not given. Both Tc and Tp significantly decreased during cooling (Figure 2). The ‘COLD – WARM 1’ difference in Tc was –1.3°C (–1.0, –1.4). A significant Tc decrease [–0.9°C (–1.2, –0.7); P < 0.05] was achieved during the first 60 min of cooling. Tc gradually increased during 120 min of rewarming. Again, a significant Tc increase [0.7°C (0.5, 1.0); P < 0.05] was achieved during the first 60 min of rewarming. The difference between Tc and Tp did not change significantly during the study.

Central haemodynamics and metabolism (Table 2)
Systemic vascular resistance (SVR) increased during cooling and then decreased after rewarming (Figure 3). The difference between SVR (COLD) and SVR (WARM 1) correlated significantly and negatively with the corresponding difference in Tc ($r^2 = 0.69$; P < 0.05), but not with the corresponding difference in Tp ($r^2 = 0.16$; P = NS). As a result of the increased SVR during cooling, MAP increased. Cardiac filling pressures (both CVP and PAOP) remained unchanged during the study. Cooling was also associated with a significant decrease in heart rate (HR) and cardiac output (CO), while stroke volume remained unchanged [48 ml/m² (40, 51) at WARM 1; 44 ml/m² (41, 46) at COLD; and 45 (43, 50) ml/m² at WARM 2; P = NS].

Unlike MAP, mean pulmonary arterial pressure remained stable. Similarly, pulmonary vascular resistance (PVR) increased to a much lesser extent than did SVR [283 dyn/s/cm⁵/m² (202; 331) at WARM 1; 285 dyn/s/cm⁵/m² (242, 337) at COLD; and 293 dyn/s/cm⁵/m² (200, 345) at WARM 2; P = NS]. Systemic DO₂, VO₂ and VCO₂, as well as REE, all significantly decreased during cooling.

The remaining parameters reflecting systemic metabolism and oxygenation, including arterial lactate, arterial and mixed venous haemoglobin oxygen saturation, and syst O₂ER, did not change throughout the study. Haemoglobin concentration did not change [88 g/l (76, 94) at WARM 1; 89 g/l (78, 96) at COLD; and 90 g/l (75, 95) at WARM 2; P = NS]. Arterial pH was stable [7.43 (7.39, 7.46) at WARM 1; 7.44 (7.41, 7.47) at COLD; and 7.42 (7.41; 7.46) at WARM 2; P = NS], and glycaemia was unaltered (7.7 mmol/l (6.5, 9.4) at WARM 1; 7.5 mmol/l (6.4, 9.1) at COLD; and 7.4 mmol/l (6.9, 9.1) at WARM 2; P = NS).

Hepatosplanchnic response (Table 3)
Despite a high interindividual variability in hepatic venous haemoglobin oxygen saturation (ShvO₂, range 0.23–0.81 at WARM 1), time course studies of ShvO₂ did not show changes throughout the procedure (Figure 4). Likewise, the gradient between mixed

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**Table 2. Central haemodynamics, oxygenation and metabolism**

<table>
<thead>
<tr>
<th></th>
<th>WARM 1</th>
<th>COLD</th>
<th>WARM 2</th>
<th>P (Friedman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>91 (75, 100)</td>
<td>78 (66, 91)*</td>
<td>83 (70, 93)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>85 (84, 87)</td>
<td>91 (87, 98)*</td>
<td>86 (82, 95)**</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>13 (11, 16)</td>
<td>13 (11, 16)</td>
<td>14 (10, 14)</td>
<td>NS</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>15 (14, 18)</td>
<td>18 (17, 19)</td>
<td>17 (16, 18)</td>
<td>NS</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>27 (24, 31)</td>
<td>27 (24, 29)</td>
<td>26 (24, 29)</td>
<td>NS</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>4.15 (3.45, 4.80)</td>
<td>3.70 (2.75, 4.13)*</td>
<td>4.10 (3.15, 4.63)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>DO₂ (ml/min/m²)</td>
<td>469 (416, 512)</td>
<td>430 (371, 458)*</td>
<td>451 (408, 521)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>VO₂ (ml/min/m²)</td>
<td>163 (141, 194)</td>
<td>147 (128, 173)*</td>
<td>155 (136, 194)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>VCO₂ (ml/min/m²)</td>
<td>121 (115, 140)</td>
<td>108 (103, 128)*</td>
<td>113 (101, 132)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>REE (kcal/day)</td>
<td>2050 (1798, 2515)</td>
<td>2010 (1606, 2290)*</td>
<td>2070 (1756, 2466)**</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>5.3 (4.9, 5.5)</td>
<td>4.8 (4.7, 5.6)*</td>
<td>5.0 (4.7, 5.7)**</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>a-base excess (mmol/l)</td>
<td>1.7 (–1.1, 4.4)</td>
<td>1.6 (–1.3, 4.9)</td>
<td>1.9 (–0.3, 3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>a-lactate (mmol/l)</td>
<td>2.1 (1.9, 2.7)</td>
<td>2.4 (2.0, 2.6)</td>
<td>2.4 (1.9, 2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>99.0 (97.5, 99.0)</td>
<td>99.0 (97.7, 99.0)</td>
<td>99.0 (97.5, 99.0)</td>
<td>NS</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>73.0 (64.0, 75.2)</td>
<td>70.0 (63.5, 75.2)</td>
<td>68.0 (64.2, 76.0)</td>
<td>NS</td>
</tr>
<tr>
<td>O₂ER (%)</td>
<td>28 (25, 35)</td>
<td>29 (24, 34)</td>
<td>29 (23, 35)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are medians, 25th and 75th percentiles.

*Significant difference COLD vs WARM 1; **significant difference WARM 2 vs COLD.

MAP, mean arterial pressure; CVP, central venous pressure; PAOP, pulmonary arterial occlusion pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; DO₂, global oxygen delivery; VO₂, oxygen consumption; VCO₂, carbon dioxide production; REE, resting energy expenditure; a, arterial; SaO₂ and SvO₂, arterial and mixed venous haemoglobin oxygen saturation; O₂ERsyst, systemic O₂ extraction ratio.
venous haemoglobin oxygen saturation (SvO₂) and ShvO₂ as well as the spl O₂ER remained unchanged.

Cooling was not associated with significant changes in the hepatic venous L/p ratio nor in the arterial to hepatic venous lactate difference. Hepatic venous glucose concentrations did not change significantly [8.0 mmol/l (6.6, 9.8) at WARM 1; 7.8 mmol/l (5.9, 9.4) at COLD; and 7.6 mmol/l (6.9, 9.0) at WARM 2; P = NS]. In addition, there was no notable change in the hepatic venous – arterial PCO₂ difference. The gastric mucosal to arterial PCO₂ difference remained stable throughout the study.

**Discussion**

The main findings of the present study are that the MCC during CVVH in septic intensive care unit (ICU) patients affected (i) neither hepatosplanchnic oxygen nor energy balance (documented primarily by unchanged ShvO₂ and the hepatic L/p ratio, respectively); (ii) nor gastric mucosal energy balance (indicated by unchanged gastric mucosal to arterial PCO₂ difference; PCO₂ gap); (iii) whereas significant changes occurred in central haemodynamics.

Because the aim of our study was to mimic a clinically relevant situation in CVVH, we warmed, cooled and then rewarmed (to 37°C) the SF and RB but did not use any other method of temperature manipulation. This procedure produced only a mild decrease in Tc. Nevertheless, we observed significant increases in SVR and MAP, and decreases in CO and HR. These findings as well as the decrease in measured global oxygen consumption (VO₂) during MCC are consistent with previous studies examining effects of temperature changes during CRRT in ICU patients [8–10]. The SVR increase on cooling was demonstrated previously in healthy animals and humans as well as in chronic

### Table 3. Hepatosplanchnic oxygen and energy balance

<table>
<thead>
<tr>
<th></th>
<th>WARM 1</th>
<th>COLD</th>
<th>WARM 2</th>
<th>P (Friedman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ShvO₂ (%)</td>
<td>51.0 (44.0, 59.5)</td>
<td>49.0 (42.0, 58.0)</td>
<td>51.0 (46.0, 57.0)</td>
<td>NS</td>
</tr>
<tr>
<td>SvO₂–ShvO₂ (%)</td>
<td>18.0 (12.8, 30.0)</td>
<td>18.0 (11.5, 29.5)</td>
<td>17.0 (10.5, 27.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Spl O₂ER (%)</td>
<td>49 (41, 55)</td>
<td>47 (42, 57)</td>
<td>48 (43, 55)</td>
<td>NS</td>
</tr>
<tr>
<td>HV lactate to pyruvate ratio</td>
<td>11 (9, 13)</td>
<td>13 (9, 17)</td>
<td>13 (10, 15)</td>
<td>NS</td>
</tr>
<tr>
<td>A – HV lactate difference (mmol/l)</td>
<td>0.59 (0.37, 0.84)</td>
<td>0.54 (0.52, 0.85)</td>
<td>0.56 (0.40, 0.95)</td>
<td>NS</td>
</tr>
<tr>
<td>HV base excess (mmol/l)</td>
<td>2.6 (–0.3, 4.6)</td>
<td>3.0 (0.9, 5.1)</td>
<td>2.5 (1.5, 5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>PCO₂ gap (kPa)</td>
<td>1.3 (1.1, 1.9)</td>
<td>1.5 (1.3, 1.9)</td>
<td>1.4 (0.8, 1.7)</td>
<td>NS</td>
</tr>
<tr>
<td>HV – A PCO₂ difference (kPa)</td>
<td>0.7 (0.6, 0.9)</td>
<td>0.9 (0.6, 1.2)</td>
<td>0.7 (0.5, 1.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are medians, 25th and 75th percentiles.

A, arterial; HV, hepatic venous; ShvO₂, hepatic venous haemoglobin oxygen saturation; SvO₂, mixed venous haemoglobin oxygen saturation; spl O₂ER, splanchnic oxygen extraction ratio; PCO₂ gap, gastric mucosal to arterial PCO₂ difference.

**Fig. 3.** Time course of systemic vascular resistance index (SVRI).

**Fig. 4.** Individual changes in hepatic venous haemoglobin oxygen saturation (ShvO₂). Dashed line, patient without norepinephrine.
dialysis patients [1,3,4]. This increase was explained mainly by elevations in skin and/or muscle vascular resistance, presumably due to the increased endogenous norepinephrine production [17]. However, Beerenhout et al. [18] also found reduced nitric oxide release when cooler dialysates were used.

In our study, the relative changes in SVR correlated significantly and negatively with relative changes in Tc. Recently, van der Sande et al. [5] compared thermal and haemodynamic effects of intermittent isolated ultrafiltration (UF) with UF + haemodialysis at different dialysate temperatures. They found that haemodynamic changes were related not only to lower Tcs, but also to the amount of heat loss in the extracorporeal circuit (ECC), i.e. to the negative energy transfer. At present, the amount of energy transfer in ECC during IHD can be measured with special devices, such as a blood temperature monitor (Fresenius Medical Care, Bad Homburg, Germany). However, to our knowledge, these monitors are not yet available for CRRT machines. The consequence of heat loss in ECC is a lower temperature of RB which in turn may activate compensatory mechanisms, such as skin vasoconstriction and endogenous heat production. Although we did not measure energy transfer in the ECC directly, we presume that it was negative during cooling for at least two reasons. First, we achieved a significant decrease in Tc during cooling (the hypothermic treatment) and, secondly, the decrease in peripheral temperature indicated decreased heat dissipation through the skin. Interestingly, we found a mild decrease in REE measured by indirect calorimetry. This decrease in heat production during cooling was probably influenced by sedation in our patients, which may have counterbalanced the compensatory endogenous mechanisms (see above).

From these findings, we suggest that precise assessment of heat balance during RRT would require concomitant measurements of (i) energy transfer in ECC; (ii) heat dissipation; and (iii) endogenous heat production, while remembering that absolute values of REE measured by indirect calorimetry may be underestimated due to carbon dioxide losses in the haemofilter [19].

Previous studies examining temperature changes during renal replacement therapies (RRTs) assessed mainly time course changes in systemic haemodynamics [1–5]. Our study extended these findings by evaluating responses of the HSR to MCC. During MCC, ShvO$_2$ was unchanged compared with the ‘warm’ periods, despite the decrease in DO$_2$-syst . In addition, spl O$_2$-ER and the SvO$_2$–ShvO$_2$ gradient did not change during these periods [20]. There are two principle variables that may influence ShvO$_2$, spl O$_2$-ER or both during MCC provided that arterial oxygen content remains unchanged, which was the case in our study. These variables are changes in the total hepatosplanchnic blood flow (HSBF) or in splanchnic VO$_2$. Since we did not directly measure HSBF or splanchnic VO$_2$, we cannot state whether these variables changed even though ShvO$_2$ remained stable.

In theory, cooling may have caused a left shift in the oxyhaemoglobin dissociation curve, which may impair spl O$_2$-ER [21]. However, several findings in our study argue against this possibility. The hepatic venous L/p ratio, the arterial to hepatic venous lactate difference and hepatic venous acid–base status all remained unchanged during MCC, which precluded any profound derangements in energy metabolism of hepatic vein-drained viscera and/or the occurrence of tissue dysoxia in the HSR [15]. Moreover, the gastric mucosal to arterial PCO$_2$ difference, which provides a surrogate for adequacy of gastric mucosal perfusion and energy balance, remained unchanged during the procedure [16]. Taken together, and independent of potential changes in HSBF and/or splanchnic oxygen consumption, our results suggest that the oxygen and energy supply to demand ratio in HSR was not worsened by CRRT-induced MCC. This was supported further by the stable hepatic venous to arterial PCO$_2$ difference, indicating that splanchnic blood flow was high enough to wash out CO$_2$ produced in the hepatosplanchnic area during MCC.

As was mentioned previously, the gastric mucosal to arterial PCO$_2$ difference did not change or showed only mild increases in four patients during MCC, suggesting an unaltered gastric mucosal energy balance. There are very few comparable data on the time course of the PCO$_2$ gap during RRT. John et al. [22] found only mild increases in the PCO$_2$ gap after 24 h of CVVH despite decreases in Tc (mean Tc decrease = 1.9°C after 24 h) in septic shock patients. Certain indirect comparisons could be made with human studies evaluating the time course of the PCO$_2$ gap during and after cardiopulmonary bypass (CPB). The results from Croughwell et al. [23], who compared hypothermic with tepid CPB with lower constant flow in a hypothermic group, and those of Thoren et al. [24] suggested that gastric mucosal energy balance may not be worsened when patients are cooled. Interestingly, Kutilla et al. [25] found opposite behaviours in skin and stomach perfusion during rewarming after hypothermic CPB, supporting the idea that skin and splanchnic blood flow do not always change in the same direction during changes in patient core temperatures. However, they achieved a more profound hypothermia and used a different patient population from that in the present study.

The present findings, we believe, may have important clinical implications. MCC induced by CVVH does not appear to be harmful with respect to global and splanchnic energy metabolism. The haemodynamic goals, such as CO, may differ according to patient temperature since hepatosplanchnic energy metabolism and oxygen balance may be well maintained during MCC even if absolute values of CO are lower than during ‘warming’. Nevertheless, clinicians should bear in mind that MAP has a limited value as the only surrogate for haemodynamic stability during RRT. Accordingly, Jacob et al. [26] found a significant decrease in CO and HSBF despite stable MAP values during IHD in ICU patients.
The present study has certain limitations. We studied only short-term (2 h) effects of CRRT-induced MCC in septic ICU patients who were all hyperthermic before CVVH initiation. Therefore, the impact of CVVH-induced MCC may be different in other patient populations, including those having a low flow state, or conscious patients without pharmacological sedation.

It is very likely that the effects of CVVH-induced MCC in septic ICU patients are not limited to haemodynamic and metabolic changes. When given in pre-dilution mode, SFs at lower temperatures result in lower blood temperatures circulating through the haemofilter, which in turn may have beneficial effects on biocompatibility (thrombogenity, complement activation, need for anticoagulation), as has been demonstrated in chronic dialysis patients [27]. In addition, more profound hypothermia may have negative effects on immune system status. Hence, further experimental work is needed to determine whether temperature manipulation is of benefit in certain stages of sepsis. Moreover, we believe that it would be challenging to investigate the haemodynamic and metabolic effects of other cooling modalities such as cold blankets or new intravascular cooling devices (without a haemofilter).

We conclude that MCC during standard CVVH may not affect hepatosplanchnic oxygen and energy balance in septic mechanically ventilated critically ill patients, even though it has significant effects on global haemodynamics and metabolism.

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