Nephrol Dial Transplant (2001) 16: 320–327

Nephrology Dialysis Transplantation

Original Article

Effects of continuous haemofiltration *vs* intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial

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Abstract

Background. Parameters of splanchnic regional perfusion, like intramucosal pH (pHi) and pCO_2 (pCO_2i), may predict outcome in septic shock patients. Continuous venovenous haemofiltration (CVVH) has been considered beneficial in haemodynamically unstable septic shock patients. In a prospective, randomized, clinical study, we investigated whether CVVH, in comparison to intermittent haemodialysis (IHD), is able to improve splanchnic regional perfusion in critically ill patients.

Methods. Thirty septic shock patients with acute renal failure were randomized to either CVVH ($n=20$) or IHD ($n=10$) groups for renal replacement therapy. Patient characteristics at baseline were not different in terms of severity of illness (APACHE II scores), haemodynamics, and pHi/pCO_2i values. Systemic haemodynamics, oxygen transport variables, and splanchnic regional perfusion parameters were measured at 0.5, 2, 4 and 24 h after initiation of renal replacement therapy. There were no major changes in vasopressor support throughout the 24-h study period.

Results. In contrast to IHD, CVVH caused a decrease in heart rate (-3 ± 11 *vs* $+9\pm8$/min, $P<0.01$) and an increase in systolic blood pressure ($+12\pm1$ *vs* -5 ± 17 mmHg, $P<0.05$) after 2 h. After 24 h, increased systemic vascular resistance was found in the CVVH group in comparison with the IHD group ($+312\pm755$ *vs* -29 ± 89 dyne/cm^5, $P<0.05$) and was accompanied by a decrease in cardiac output (-1.54 ± 1.4 *vs* -0.25 ± 0.9 l/min, $P<0.01$). However pHi values remained constant throughout the 24-h study period in both groups and were not different between the groups (CVVH 7.19 ± 0.1 *vs* IHD 7.19 ± 0.1, n.s.) as did the pCO_2i values (CVVH $+7\pm17$ *vs* IHD 0 ± 15 mmHg, n.s.) and pCO_2 gap values (CVVH $+6\pm15$ *vs* IHD $+5\pm12$ mmHg, n.s.).

Conclusions. Despite different changes of systemic haemodynamics between CVVH and IHD, CVVH did not improve parameters of splanchnic regional perfusion like pHi, pCO_2i or pCO_2 gap in septic shock patients.

Keywords: acute renal failure; continuous haemofiltration; haemodynamics; intramucosal acidosis; oxygen transport; splanchnic regional perfusion

Introduction

Septic shock and multiple organ failure, including acute renal failure, are leading causes of morbidity and mortality in the critical care setting. The mortality rate in these patients ranges from 40 to 80% [1]. Continuous renal replacement therapies, introduced by Kramer *et al.* [2] are widely used in the treatment of acute renal failure in critical care. Improved cardiovascular stability, easier fluid removal, and superior metabolic control during continuous venovenous haemofiltration (CVVH) in comparison to intermittent haemodialysis (IHD) has been demonstrated in retrospective comparisons [3,4]. Moreover, recent studies have suggested that CVVH may remove proinflammatory substances, including endotoxin, cytokines, oxygen free radicals, and arachidonic acid metabolites from the circulation of septic patients [5,6]. Therefore CVVH may represent another aspect of immunotherapy [9]. However, whether these possible advantages of CVVH in comparison with IHD also improve mortality or outcome in these patients has not yet been established [7,8]. Most outcome studies have been flawed by patient severity mismatch or retrospective design, differing

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renal replacement techniques or different kidney membranes.

In septic shock and multiple organ dysfunction syndrome the release of various mediators can be involved in reduction of myocardial contractility, increase in oxygen demand, and alteration in oxygen extraction capabilities, all leading to the development of tissue acidosis [9]. However, global indices of oxygen delivery and consumption provide no useful information as to the adequacy of tissue oxygenation. Splanchnic hypoperfusion occurs early in septic shock and may occur before the usual indicators of shock are present, such as hypotension or lactic acidosis [9,10]. Gut mucosal ischaemia increases gut permeability, alters gut immune function, and increases translocation of bacteria and various inflammatory mediators [11]. This process has been postulated to play an important role in the development of the multiple organ dysfunction syndrome. Therefore, maintaining splanchnic perfusion may reduce complications and improve the outcome of critically ill patients [12].

The measurement of gastric intramucosal pH (pHi) and local pCO_2 production (pCO_2i) by gastric tonometry has been shown to be a valuable technique to assess the adequacy of perfusion of the gastrointestinal mucosa, and to have a high predictive value for estimating outcomes in critically ill patients [13–15]. Furthermore it has been demonstrated that maintaining pHi in the normal range may improve the outcome of critically ill patients [16].

As gastric tonometry and the regional perfusion values derived by this method seem to be valuable markers of patient outcome, we investigated whether CVVH could improve gastric intramucosal acidosis as a central marker of haemodynamic stabilization, immunomodulating therapy, and of possible outcome improvement induced by CVVH in comparison with IHD. We studied septic shock patients with acute renal failure in a prospective, controlled, randomized clinical study to determine the influence of CVVH *vs* IHD on these parameters of splanchnic regional perfusion.

Materials and methods

Patients

All patients admitted to our medical intensive care unit over a 2-year period were eligible for the study if they fulfilled the following inclusion criteria: age between 18 and 80 years, body weight between 50 and 100 kg, presence of acute renal failure (ARF) (serum creatinine >3.0 mg/dl and/or urine output <10 ml/h), presence of severe septic shock according to the criteria of the ACCP/SCCM consensus conference [17], need for mechanical ventilation for more than 48 h (Evita 2, Dräger AG, Lübeck, Germany), severe illness defined by an APACHE II score between 20 and 45, pulmonary capillary wedge pressure ⩾12 mmHg but <18 mmHg to exclude severe fluid overload or fluid deficit, no history of chronic renal insufficiency (serum creatinine <2.0 mg/dl before ARF). Patients were excluded from the study when they met any of the following criteria: life-threatening electrolyte disorders that made IHD mandatory, surgical procedures that had to be performed during the 48 h following admission, concomitant participation in any other trial, a clearly irreversible condition with an expected rapidly fatal course during the next 48 h or the decision to limit treatment. Patients had to be free of all forms of renal replacement therapy 12 h before inclusion. Only noradrenaline was used as vasopressor support in all patients to maintain mean arterial pressure (MAP) at approximately 70 mmHg prior to the study. The underlying pathology of septic shock was treated with antibiotics as appropriate for the primary source of infection or isolated micro-organism.

Thirty-three patients were eligible for enrolment according to the inclusion criteria. Three patients had to be excluded from the study, one because of severe hyperkalaemia that made rapid IHD treatment necessary, and two patients because of an expected rapidly fatal course over 48 h. Thus, thirty patients were enrolled in this prospective, randomized, controlled clinical study (Figure 1). Table 1 shows the underlying pathology of these septic shock patients. They were assigned by a randomization list in a 2:1 fashion to the CVVH ($n=20$) or the IHD ($n=10$) group. Seventeen patients (11 in the CVVH and six in the IHD group) had already received renal replacement therapy for ARF, but not during the 12 h prior to the study. Baseline characteristics at study entry such as systemic haemodynamic variables, parameters of the actual fluid and pH status, parameters of the splanchnic microcirculation and catecholamine dosages were not different between the CVVH and the IHD groups (Table 2).

Study design

The study was approved by the Ethics Committee of the University of Erlangen-Nürnberg. Written informed consent was obtained from the relatives of the patients before they entered the study. If not already done, a pulmonary artery catheter was placed *via* the subclavia or the internal jugular vein and an arterial line was inserted into the radial artery. After assessment of baseline values, patients were randomized into the CVVH or IHD groups. The following measurements were obtained at baseline and after 0.5, 2, 4 and 24 h: systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), stroke volume (SV), cardiac output (CO), systemic vascular

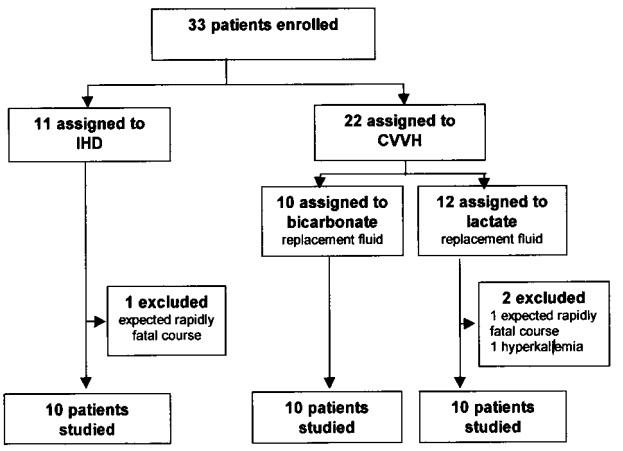

Fig. 1. Trial profile patients': patients' inclusion, randomization, exclusion.

Table 1. Underlying pathology in patients with septic shock in the CVVH and IHD groups

	CVVH	IHD
Patients (*n*)	20	10
Underlying pathology		
pneumonia	16	8
erysipelas	2	—
urosepsis	1	—
cholangitis	—	1
peritonitis	—	1
meningitis	1	—

Table 2. Baseline characteristics of the patients with septic shock in the CVVH and IHD groups

	CVVH ($n=20$)	IHD ($n=10$)
Age (years)	59 ± 12	64 ± 10
APACHE II-score	34 ± 5	33 ± 4
Sex (m/f)	17/3	9/1
Weight (kg)	84 ± 14	87 ± 10
Height (cm)	176 ± 8	177 ± 5
Temperature (°C)	38.2 ± 1.0	38.1 ± 0.4
Blood pressure (mmHg)		
systolic	116 ± 20	120 ± 12
diastolic	50 ± 15	53 ± 10
mean	69 ± 15	75 ± 9
Heart rate (/min)	114 ± 17	108 ± 13
CVP (mmHg)	12 ± 3	10 ± 3
PCWP (mmHg)	16.7 ± 4.4	15.4 ± 4.4
Cardiac output (l/min)	8.2 ± 2	7.6 ± 2.2
Vasopressor support (noradrenaline mg/h)	2.04 ± 1.96	1.90 ± 1.67
Arterial blood gas analysis		
pH value	7.31 ± 0.10	7.30 ± 0.09
HCO_3^- (mmol/l)	18.8 ± 2.5	19.0 ± 3.5
pCO_2 (mmHg)	39 ± 8	41 ± 16
pO_2 (mmHg)	91 ± 30	101 ± 47
O_2 saturation (%)	94 ± 5	94 ± 7
Serum lactate (mg/dl)	20.8 ± 12.8	14.8 ± 5.6
Serum urea nitrogen (mg/dl)	158 ± 63	171 ± 48
Serum creatinine (mg/dl)	5.2 ± 2.6	4.9 ± 1.8

All *P* values are non-significant.

resistance (SVR), body core temperature, arterial and mixed venous blood gases (pO_2), pCO_2, oxygen saturation, bicarbonate), oxygen delivery (DO_2) and oxygen consumption (VO_2) (calculated with standard formulae), serum lactate, serum creatinine blood urea nitrogen, dosage of noradrenaline, total amount of ultrafiltration, and 24 h fluid balance.

Assessment of splanchnic microcirculation

A gastric tonometer (Trip TGS catheter, Tonometrics, Worcester, USA) was placed in each patient's stomach and correct placement was controlled by abdominal X-ray. All patients received H2 blockers, but no enteral nutrition during the study period. The tonometer balloon was inflated with physiological saline and samples were anaerobically withdrawn after $\geqslant$90 min at measurement points 2, 4 and 24 h and after 30–60 min at point 0.5 h. This time period allowed for the equilibration of pCO_2 between the gastric mucosa and the saline in the balloon. An arterial blood sample was obtained simultaneously for the determination of blood gases and bicarbonate (HCO_3^{-1}) concentration. The tonometer and blood samples were analysed at 37°C using a blood gas analyser (ABL 505, Radiometer, Copenhagen, Denmark). The measured pCO_2i was corrected according to the equilibration period (if $\geqslant$90 min no correction was necessary) and the pHi was calculated with the modified Henderson–Hasselbalch equation:

$$\mathrm{pHi} = 6.1 \pm \mathrm{Log}_{10}\ \{[HCO_3]/pCO_2 \times 0.03\}$$

The gap between the gastric intramucosal and arterial carbon dioxide tensions was calculated by the formula:

$$pCO_2\ \mathrm{gap} = pCO_2\mathrm{i} - p_aCO_2$$

This formula has been suggested to be the best estimate of mesenteric ischaemia [18]. Markers of splanchnic regional perfusion were also measured after 0.5, 2, 4 and 24 h.

Renal replacement techniques

Vascular access was obtained in all patients by insertion of a double-lumen haemodialysis catheter (Quinton Instruments, Bothell, WA, USA) into the subclavian, internal jugular or femoral vein by standard Seldinger technique. Biocompatible polysulphone membranes were used in IHD as well as in CVVH. The fluid intake due to nutrition and medication was approximately 2.0–2.6 litres/day. Fluid removal by ultrafiltration during renal replacement therapy was calculated to be approximately 1.2–1.8 litres during the 24-h study period so as to match the fluid intake from nutrition and medication in 24 h minus 800 ml of insensible losses. In the case of severe hypotensive episodes during renal replacement therapy (defined as a fall in MAP >20% from baseline) a fluid challenge of 250 ml normal saline was administered until blood pressure was controlled. If possible this extra fluid was removed during the remaining study period. An effort was made to keep asopressor support constant during the 24-h study period. In the case of ongoing hypotensive episodes despite fluid challenge, vasopressor support was increased to maintain MAP not lower than 20% from baseline. Vasopressor support was decreased if MAP exceeded baseline MAP by more than 20%. Daily supplements of trace elements and vitamins were administered. Additional potassium chloride was given as required. No supplemental bicarbonate or lactate was administered during the study period.

CVVH

CVVH was performed during the 24-h study period with a roller blood pump and digital fluid balance control system (BSM 22, Hospal, Germany) using standard blood tubing lines. A high-flux polysulphone haemofilter with a cut-off point of approximately 30 kDa (AV 600, 1.35 m^2 active surface area, Fresenius, Bad Homburg, Germany) was used. Haemofilters were initially rinsed with 1 litre normal saline including 5000 IU heparin for at least 30 min. The system was then connected to the patient. Anticoagulation of the extracorporal circuit was achieved using a loading dose of 1000 IU heparin followed by an individual patient-adjusted anticoagulation regimen based on the activated clotting time (100–120 s). Blood flow was maintained at approximately 250 ml/min. After 10 min, high volume ultrafiltration was

achieved with a steady state rate of 2 litres/h of ultrafiltrate. To maintain fluid balance an isotonic lactate-buffered (HF23, Fresenius, Bad Homburg, Germany, $n=10$) or bicarbonate-buffered (HF-BIC 35-010, Fresenius, Bad Homburg, Germany, $n=10$) fluid was replaced continuously. Fluids were rewarmed to 37°C by a heating device and added in the postdilutional mode.

IHD

Intermittent haemodialysis was carried out during the first 4 h of the 24 h study period using a standard haemodialysis device (AK 100, Gambro, Lund, Sweden) and standard blood tubing lines. A low-flux polysulphone haemodialysis membrane with a cut-off point of approximately 5 kDa (F6HPS, 1.3 m^2 active surface area, Fresenius, Bad Homburg, Germany) was used. Initial heparin rinsing and circuit anticoagulation did not differ from CVVH. Blood flow was approximately 250 ml/min. Ultrafiltration rate was 250–500 ml/h to achieve a negative fluid balance that matched approximately the fluid intake during the 24-h study period minus 800 ml of insensible losses. A bicarbonate-buffered dialysate was used during IHD.

Statistical analysis

A sample size of $n=8$ in each group was calculated prior to the study to detect a difference in pHi values of 0.1 between different renal replacement therapies (normal value ≈ 7.34) with a type-1 error of $\alpha=0.05$ and a type-2 error of $\beta=0.2$, assuming a standard deviation of pHi in control subjects of 0.08. Changes from baseline in the value of any given variable over time within one group were analysed firstly by non-parametric analysis of variance (Friedman's test). If Friedman's test was positive, *post-hoc* analysis with Wilcoxon's test with adjustment for multiple comparisons was performed to test whether any one time point was different from another. For across-group comparisons (IHD value at time *x vs* CVVH value at time *x*) the Mann–Whitney U test was used. All data are expressed as the absolute change $\pm$SD from the corresponding baseline. Two-sided *P* values are presented herein. A two-sided *P* value <0.05 was considered statistically significant.

Results

Systemic haemodynamics

Heart rate at baseline was 114 ± 17/min in the CVVH group and 108 ± 13/min in the IHD group; there was no significant different between the groups. During CVVH heart rate declined after 2 h and 4 h in comparison with IHD (-3 ± 11/min and -2 ± 12/min for CVVH *vs* $+9\pm8$/min and $+9\pm8$/min for IHD, $P<0.01$). During IHD heart rate increased ($P<0.01$), (Figure 2). However, 24 h after initiation of renal replacement therapy, heart rate had returned to baseline in the IHD group and the difference between both groups was no longer observed (-9 ± 22/min for CVVH *vs* -3 ± 7/min for IHD, n.s.).

SBP was 116 ± 20 mmHg in the CVVH group and 120 ± 12 mmHg in the IHD group at baseline. An increase in SBP was observed after 0.5 and 2 h of CVVH in contrast to IHD, where SBP decreased ($+8\pm20$ and $+12\pm19$ mmHg for CVVH *vs* -12 ± 16 and -5 ± 17 mmHg for IHD, $P<0.05$) (Figure 2). Again, this difference was not observed after 24 h ($+5\pm30$ mmHg for CVVH *vs* -1 ± 17 mmHg for IHD, n.s.). Similar responses were observed for MAP and DBP during both forms of renal replacement therapy (data not shown).

More severe hypotensive episodes (decrease in MAP >20% from baseline) during renal replacement therapy with the consequent extra fluid challenge occurred in nine patients of the CVVH group (45%) and in six patients of the IHD group (60%). Four patients in the CVVH group and four patients in the IHD group did not respond sufficiently to the fluid challenge, therefore vasopressor support had to be increased during the study period. Vasopressor support was subsequently decreased in three patients during CVVH and in one patient during IHD.

The amount of vasopressor support was not different between the groups at baseline (noradrenaline 2.04 ± 1.96 mg/h for CVVH *vs* 1.90 ± 1.57 mg/h for IHD, n.s.). There were no major changes in the amount of vasopressor support during the study period in the CVVH group (0.5 h, 2.10 ± 1.98; 2 h, 2.10 ± 1.98; 4 h, 2.12 ± 1.88 mg/h) nor in the IHD group (0.5 h, 2.06 ± 1.91; 2 h, 2.16 ± 1.78; 4 h 2.14 ± 1.94 mg/h), and no differences between the two groups after 24 h (2.18 ± 1.79 mg/h for CVVH *vs* 1.98 ± 1.68 mg/h for IHD, n.s.).

The total amount of net fluid removal during the 24 h of renal replacement therapy was not different between the groups (-1680 ± 360 ml for CVVH *vs* -1520 ± 440 ml for IHD, n.s.), neither was patients'

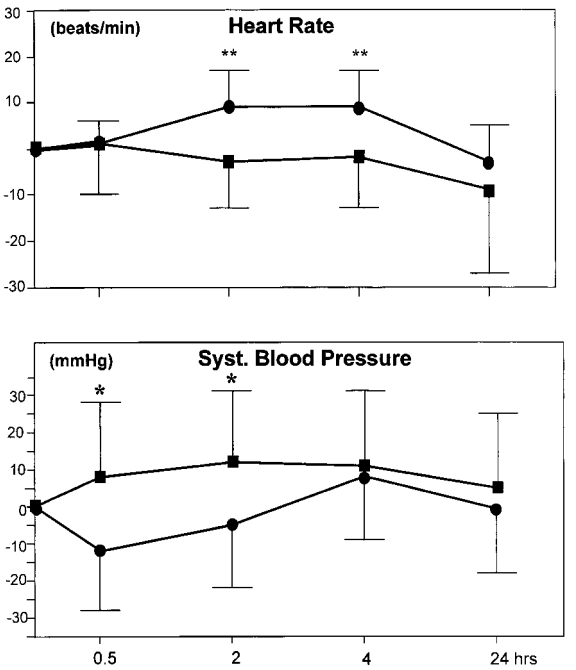

Fig. 2. Changes from baseline in heart rate (upper) and systolic blood pressure (lower) during the 24-h study period in the CVVH (■) and IHD (●) groups. *$P<0.05$, **$P<0.01$.

total 24 h fluid balance (+668±389 ml for CVVH *vs* +704±423 ml for IHD, n.s.).

PCWP was 16.7±4.4 mmHg in the CVVH group and 15.4±4.4 mmHg in the IHD group at baseline, which was not different between the groups. In both groups PCWP decreased moderately with a maximum decrease after 2 h and a return towards baseline after 24 h. There was no difference in PCWP between the groups (PCWP after 24 h, −2.1±3.2 mmHg for CVVH *vs* −1.3±4.4 mmHg for IHD, n.s.).

CO was not different between the CVVH group (8.2±2.0 l/min) and the IHD group (7.6±2.2 l/min) at baseline. After initiation of renal replacement therapy CO decreased in both groups during the first hours (Figure 3). When haemodialysis was terminated in the IHD group, CO values rose after 4 h and returned to baseline after 24 h. In the CVVH group CO declined further and was lower than at baseline and in comparison with the IHD group after 24 h (−1.54±1.4 l/min for CVVH *vs* −0.25±0.9 l/min for IHD, $P<0.01$). SVR at baseline was 586±40 dyne×s×cm^{-5} in the CVVH group and 752±237 dyne×s×cm^{-5} in the IHD group (n.s.). As CO declined, SVR increased during CVVH in comparison to IHD after 24 h (+312±755 in CVVH *vs* −29±89 dyne×s×cm^{-5}, $P<0.05$). In the IHD group SVR was not different after 24 h in comparison to baseline (Figure 3).

There was no difference in patients' core temperature between the CVVH and IHD groups (38.2±1.2°C for CVVH *vs* 38.1±0.7°C for IHD, n.s.). While temperature did not change during IHD there was a decrease in core temperature after 30 min of CVVH (−0.5±0.4°C for CVVH *vs* −01±0.3°C for IHD, $P<0.01$). During the following 24 h we noticed a continuous decline in core temperature in comparison with baseline and with IHD after 24 h (−1.9±0.8°C for CVVH *vs* −0.3±1.3°C for IHD, $P<0.001$) (Figure 3).

Systemic acid–base status

Arterial pH values and arterial bicarbonate levels at baseline were not different between the CVVH and IHD groups. During CVVH and IHD arterial pH increased constantly, as did arterial bicarbonate levels. After 24 h these increases were sustained in the CVVH group but not in the IHD group (Table 3).

Arterial CO_2 tension was not different between the CVVH and IHD groups at baseline. There were no major changes in arterial CO_2 tension during the study period in either group (Table 3).

Oxygen transport

Arterial oxygen tension (paO_2) and mixed venous oxygen tension (pvO_2) were not different between the groups at baseline and did not change during the study period in either group (data not shown). DO_2 was 1043±220 ml/min in the CVVH group and 911±201 ml/min in the IHD groups (n.s.). There was a decrease in DO_2 during CVVH related to the decrease in CO (DO_2 after 24 h, –174±197 ml/min for CVVH *vs* −6±131 ml/min for IHD, $P<0.01$) (Figure 4). However, this decrease in DO_2 was not accompanied by a decrease of oxygen consumption VO_2. It did not change significantly in comparison to baseline in either group nor between the groups

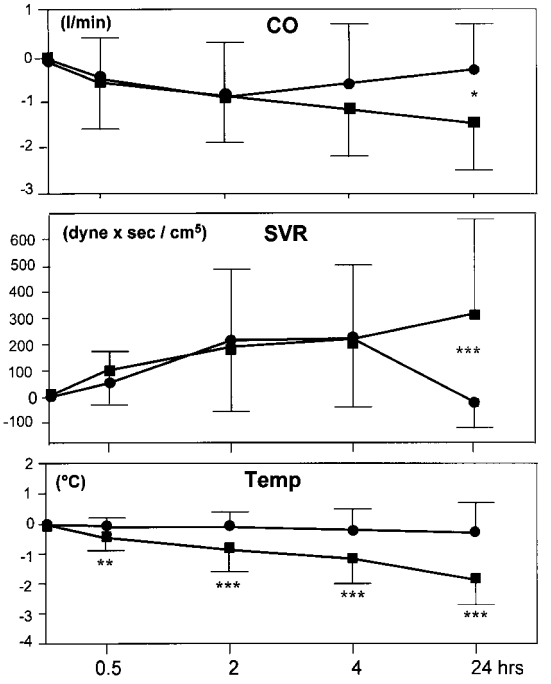

Fig. 3. Changes from baseline in cardiac output (CO), systemic vascular resistance (SVR), and body core temperature (Temp) during the 24-h study period in the CVVH(■) and IHD (●) groups. *$P<0.01$, **$P<0.001$.

Table 3. Changes in parameters of the systemic acid–base status during the study period in the CVVH and the IHD groups

	pH		HCO_3^-		PCO_2	
	CVVH	IHD	CVVH	IHD	CVVH	IHD
Baseline	7.31±0.10	7.30±0.09	18.8±2.5	19.0±3.5	39.1±8.2	41.8±18.1
0.5 h	7.32±0.11	7.31±0.08	+0.8±3.0	+1.7±1.3	−0.6±6.0	+1.8±5.3
2 h	7.33±0.12	7.35±0.09	+1.0±2.3	+3.2±2.3	+0.2±3.3	+1.4±6.3
4 h	7.32±0.10	7.36±0.09	+0.4±1.6	+3.6±2.4	−0.3±3.9	+0.6±7.4
24 h	7.35±0.08	7.34±0.05	+2.0±2.0	+0.3±1.7	+1.2±7.4	−3.6±12.2

Changes between the groups did not reach significance.

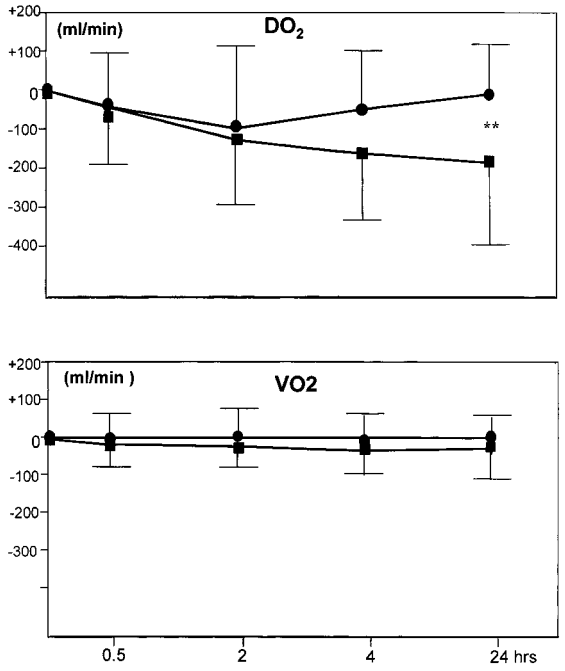

Fig. 4. Changes in oxygen delivery (DO_2) and oxygen consumption (VO_2) during the 24-h study period in the CVVH (■) and IHD (●) groups. $^*P<0.01$.

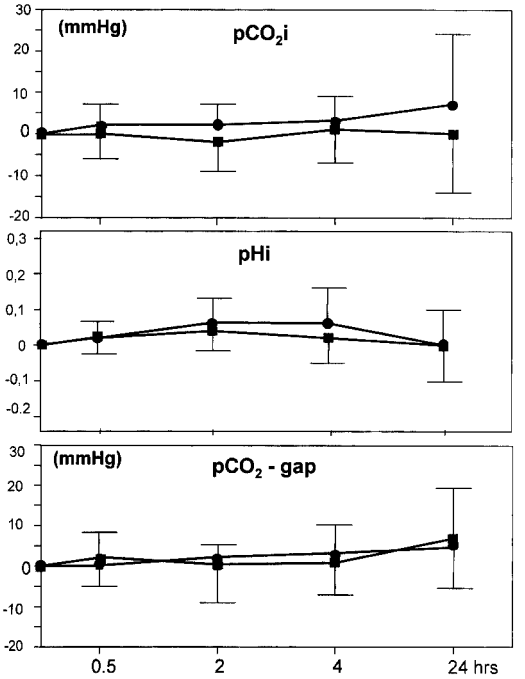

Fig. 5. Changes from baseline in intramucosal pCO_2 (pCO_2i), intramucosal pH (pHi) and intramucosal–arterial pCO_2 gap during the 24-h study period in the CVVH (■) and IHD (●) groups.

(Figure 4). Therefore oxygen extraction ratio (O_2ER) increased mildly in the CVVH group in comparison with baseline and in comparison with IHD, where it remained unaffected (O_2ER after 24 h, $+5\pm10\%$ for CVVH *vs* $0\pm5\%$ for IHD, n.s.).

Serum lactate levels were 20.8 ± 12.8 mg/dl in the CVVH group and 14.8 ± 5.6 mg/dl in the IHD group at baseline (n.s.). Serum lactate increased during CVVH in comparison with baseline and in comparison with IHD, the group in which levels remained constant (after 24 h, $+10.1\pm10.5$ mg/dl *vs* 2.2 ± 6 mg/dl for IHD, $P<0.05$). This increase in serum lactate occurred mainly in those patients treated with a lactate-buffered replacement solution (after 24 h, $+16.5\pm21.0$ mg/dl for the lactate *vs* $+5.4\pm20.3$ mg/dl for the bicarbonate replacement group).

Gastric tonometry derived values

There was no difference in pCO_2i between groups at baseline (51 ± 13 mmHg for CVVH *vs* 53 ± 15 mmHg for IHD, n.s.). During the 24 h of all renal replacement therapies there was no significant change in pCO_2i in the groups, either in comparison to baseline or between the groups (after 24 h, 7 ± 17 mmHg for CVVH *vs* 0 ± 15 mmHg for IHD, n.s.) (Figure 5). In the CVVH group pHi was 7.19 ± 0.1 and in the IHD group pHi was 7.19 ± 0.09 (n.s.). There were no significant changes in pHi values during the 24-h study period; after 24 h pHi values were the same as at baseline (7.19 ± 0.1 in CVVH *vs* 7.19 ± 0.08 in IHD, n.s.) (Figure 5). The gap between the arterial and the intramucosal pCO_2 (pCO_2 gap) was 13 ± 12 mmHg in the CVVH and 11 ± 8 mmHg in the IHD group (n.s.). During renal replacement therapy the pCO_2 gap increased slightly in both groups and was higher in both groups after 24 h in comparison to baseline ($P<0.05$), but there were no differences between groups ($+6\pm15$ mmHg for CVVH *vs* $+5\pm12$ mmHg for IHD, n.s.) (Figure 5).

Changes of systemic haemodynamic variables and gastric tonometry-derived values pHi, pCO_2i, and pCO_2 gap described for the CVVH group were not influenced by the use of different replacement fluids (bicarbonate or lactate) as results were not different between these subgroups (data not shown).

Serum creatinine and urea nitrogen

At baseline serum urea nitrogen (SUN) was 158 ± 63 mg/dl for CVVH and 171 ± 48 mg/dl for IHD (n.s.). After 24 h of renal replacement therapy SUN declined to 112 ± 57 mg/dl in the CVVH group and to 143 ± 43 mg/dl in the IHD group (difference between groups n.s.). Serum creatinine was 5.2 ± 2.6 mg/dl for CVVH and 4.9 ± 1.8 mg/dl for IHD (n.s.) at baseline and 3.5 ± 1.8 mg/dl for CVVH and 4.5 ± 1.8 mg/dl for IHD ($P<0.01$) after 24 h of renal replacement therapy.

Complications and mortality

Hypotensive episodes, defined as a fall in MAP >20% from baseline, were noted in the IHD group in six patients and in the CVVH group in nine patients. Although the study period was only 24 h we followed the included patients during their course of critical illness. All patients remained on the randomized renal

replacement therapy mode during the following days or weeks. In the CVVH group we noted a recurrent premature filter clotting in three patients. Another three patients treated with CVVH experienced bleeding complications. One patient had a severe intracerebral haemorhage and two other patients had minor epistaxis. Intensive care unit mortality rate was 70% in both groups.

Discussion

In this randomized, prospective, controlled clinical trial in patients with severe septic shock we investigated the effects on systemic haemodynamics and splanchnic regional perfusion of CVVH in comparison to IHD. We demonstrated a favourable effect of CVVH on systemic haemodynamics in comparison to haemodialysis. However, splanchnic regional perfusion remained unaffected and was not different between the renal replacement therapies.

In our study an increase in heart rate was accompanied by a fall in blood pressure during the first hours of IHD. In contrast, blood pressure increased during the first hours of CVVH. The difference between the two groups was significant. Not surprisingly, more hypotensive episodes were noted during IHD than during CVVH.

Since there was no major difference in the amount of vasopressor support between the groups throughout the study period, the hypotension noticed during IHD may be explained by the faster removal of the same amount of fluid during IHD in comparison to CVVH. However the different speed of fluid removal was not mirrorred by different PCWP during the first hours of renal replacement therapy. PCWP declined mildly and similarly during the first hours in both groups.

IHD in the critically ill patient has been thought to be associated with haemodynamic instability by other investigators [4,19]. This haemodynamic instability may compromise systemic oxygen delivery and may reduce even more regional oxygen delivery to the gastrointestinal tract [19]. Under these circumstances CVVH has been postulated to be the superior renal replacement method, because of its improved haemodynamic stability [4]. In our study the fall in blood pressure during the first hours of IHD was accompanied by a reduced cardiac output and oxygen delivery. However, it was not accompanied by a fall in oxygen consumption nor most importantly, by significant changes of parameters of splanchnic regional perfusion.

Hypotensive periods observed during IHD were reversed after termination of IHD and were no longer observed after 24 h. Heering *et al.* [5] also found a normalization of elevated cardiac output and decreased vascular resistance in 18 septic shock patients during the first 24 h of CVVH and also interpreted these changes as an improvement in systemic haemodynamics induced by CVVH. In contrast, Misset *et al.* [20] questioned the improved cardiovascular stability of continuous therapies. Their study failed to find any difference in the haemodynamic response between CAVH and IHD in non-septic patients with acute renal failure.

The decrease in cardiac output after 24 h of CVVH found in our study was related to a decrease in core temperature. Despite heating devices and rewarming of the substitution fluids a decline in core temperature is a frequent finding in patients undergoing CVVH with high ultrafiltration rate [21]. The improved, less hyperdynamic systemic haemodynamics in patients during CVVH may be explained by a physically induced fall in core temperature with a subsequent increase of systemic vascular resistance. However, it has been suggested that CVVH may remove proinflammatory substances including endotoxin, cytokines, and arachidonic acid metabolites from the circulation of septic patients [5,22], so that the fall in temperature may be supported by this removal of pyrogenic substances. Sieving coefficients for polypeptides and small proteins are different between high-flux and low-flux membranes, particularly given the various modes of transport (diffusive *vs* convective). However, various studies have demonstrated that inflammatory mediators can be removed during CVVH by convection, but they are removed mainly by membrane adsorption [6]. This removal is not important enough to result in a significant effect on plasma concentrations. Given the same membrane material and surface area of filter devices in the present study, adsorptive capacities of cytokines were supposed to be equal in the two groups. According to these considerations, cytokine removal, although not measured, should not have been significantly different between CVVH and IHD. De Vriese *et al.* [22] noticed the same haemodynamic changes during CVVH as found in our study. However, these changes in systemic haemodynamics were not related to cytokine levels in the patients studied. Therefore, further studies should elucidate whether the decline in core temperature of septic patients is due to the immunomodulating properties of CVVH or to the physical means of CVVH.

Despite improved systemic haemodynamics during CVVH we were not able to detect any improvement of parameters of the splanchnic regional perfusion as indicated by constant pHi, pCO_2i, and even increasing pCO_2 gap values in both groups.

To avoid effects of renal replacement therapies on arterial bicarbonate and CO_2 the assessment of arterial-tonometer CO_2 gap (CO_2 gap) is supposed to present the most valuable parameter to evaluate intestinal intramucosal acidosis during renal replacement therapy. This parameter is independent of the arterial bicarbonate concentration, and changes in the arterial CO_2 tension will be eliminated by equal changes in mucosal CO_2 tension [18]. In our study CO_2 gap constantly increased during the 24-h study period in both groups and was elevated after 24 h in comparison to baseline in both groups. Therefore neither CVVH nor IHD was able to improve this parameter of

splanchnic regional perfusion despite the different changes in systemic haemodynamics.

Tonometry-derived parameters of splanchnic regional perfusion have been demonstrated to be valuable markers to assess the adequacy of perfusion of the gastrointestinal mucosa [13,14], and to have a high predictive value for estimating outcomes in critically ill patients [12,14–17]. In this context the further worsening of pCO_2 gap may reflect the high mortality found in our study population, which was not different between the groups. The fact that CVVH was not able to attenuate this further decline in pCO_2 gap suggests that CVVH does not have the capability to improve outcome in septic shock patients with multiple organ dysfunction syndrome.

Several studies have compared IHD with continuous therapies in terms of survival and outcome [7,8,23]. A trend toward improved survival with continuous therapies has been reported in some studies. However, most of these studies were retrospective or non-randomized comparisons, and the continuous therapies were used predominantly in haemodynamically unstable patients who were not supposed to tolerate intermittent therapies.

In our study we prospectively investigated the effects of CVVH in comparison to IHD on changes in tissue oxygenation as a different, short-term end-point, since parameters of the splanchnic regional perfusion have been demonstrated to be valuable outcome estimates. We used polysulphone membranes in both groups and patients had the same severity of illness at baseline, as reflected by equal APACHE II scores, haemodynamic parameters, and tonometry-derived values.

In conclusion, we found that CVVH mildly improved systemic haemodynamics, as indicated by less hypotension during the first hours of renal replacement therapy and a less hyperdynamic circulatory state after 24 h in comparison to IHD. However, this improvement of systemic haemodynamics did not result in improved parameters of splanchnic regional perfusion in these patients with severe septic shock and acute renal failure.

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Received for publication: 25.10.99
Accepted in revised form: 20.6.00