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High-volume haemofiltration in human septic shock

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Abstract *Objective:* To evaluate whether high volume haemofiltration improves haemodynamics and affects serum cytokine and complement concentrations in human septic shock.
Design and setting: Randomized cross-over clinical trial in a tertiary intensive care unit.
Patients: Eleven patients with septic shock and multi-organ failure.
Interventions: Patients were assigned to either 8 h of high-volume haemofiltration (HVHF; 6 l/h) or 8 h of standard continuous veno-venous haemofiltration (CVVH; 1 l/h) in random order.
Measurements and main results: We measured changes in haemodynamic variables, dose of norepinephrine required to maintain a mean arterial pressure greater than 70 mmHg and plasma concentrations of complement anaphylatoxins and several cytokines. An 8-h period of HVHF was associated with a greater reduction in norepinephrine requirements than a similar period of CVVH (median reduction: 10.5 vs. 1.0 μg/min: $p = 0.01$; median percentage reduction: 68 vs. 7 %; $p = 0.02$). Both therapies were associated with a temporary reduction ($p < 0.01$) in the plasma concentration of C3a, C5a, and interleukin 10 within 2 h of initiation. HVHF was associated with a greater reduction in the area under the curve for C3a and C5a ($p < 0.01$). The concentration of the measured soluble mediators in the ultrafiltrate was negligible.
Conclusions: HVHF decreases vasopressor requirements in human septic shock and affects anaphylatoxin levels differently than standard CVVH

Keywords Haemofiltration · Shock · Sepsis · Septic shock · Acute renal failure · Haemodialysis · Multi-organ failure

Introduction

The activation and amplification of the immune response in septic shock appears to depend on the production and release of pro-inflammatory, water-soluble small and middle molecules [1, 2, 3]. Attenuating the systemic effects of these inflammatory mediators is a logical goal of adjuvant therapy in sepsis. Unfortunately, the results of targetting single mediators during established septic shock have been disappointing [4]. Therapies aimed at simultaneously reducing the plasma concentration of several circulating inflammatory mediators may prove more effective. Continuous haemofiltration is one of these therapies. "Standard" haemofiltration (exchange rates of 1–2 l/h) has often improved cardiopulmonary function in septic patients independent of fluid balance but has failed to achieve adequate mediator removal [5, 6, 7, 8, 9, 10, 11]. Accordingly, an in-

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Table 1 Clinical features of trial patients (*APACHE II* Acute Physiology and Chronic Health Evaluation score II on ICU admission, *SAPS II* Simplified Acute Physiology Score II on ICU admission. *MRSA* methicillin-resistant *Staphylococcus aureus*)

Patient no.	Age (years)	Gender	Diagnosis	Microbiology	APACHE II	SAPS II	Outcome
1	46	M	Endocarditis	Coagulase-negative *Staphylococcus*	20	40	Survived
2	66	F	Aspiration pneumonia	*Escherichia coli*, MRSA	44	89	Died
3	74	M	Nosocomial pneumonia	MRSA	26	59	Died
4	67	F	Perforated bowel	*Citrobacter freundii*, MRSA	20	48	Died
5	69	M	Nosocomial pneumonia	Negative	27	50	Died
6	41	M	Nosocomial pneumonia	*Klebsiella pneumoniae*, MRSA	28	55	Survived
7	67	M	Caecal abscess	Negative	15	27	Survived
8	75	M	Nosocomial pneumonia	*Enterococcus faecium*, MRSA	24	58	Died
9	64	M	Empyema	*Staphylococcus aureus*	21	35	Died
10	58	F	Perforated ileum	*Escherichia coli*	25	42	Survived
11	67	M	Pneumonia	*Pneumococcus*	25	52	Survived

crease in the rate of plasma water exchange has been proposed and is supported by initial animal experiments. High-volume haemofiltration (6 l/h) in porcine and canine endotoxic shock improves arterial blood pressure and cardiac output [12, 13, 17]. Thus we hypothesized that more intensive plasma water exchange in the form of high volume haemofiltration would yield greater haemodynamic benefits than standard continuous veno-venous haemofiltration (CVVH) in patients with septic shock. We further hypothesized that HVHF would have a greater effect than CVVH on the serum concentration of cytokines and complement anaphylatoxins.

Materials and methods

Study population

Table 1 summarizes the clinical features of the 11 trial patients. Informed consent was obtained from each patient's next of kin. Patient inclusion criteria included the presence of septic shock (diagnosed according to the criteria of Bone [14], established acute renal failure secondary to septic shock (with oliguria or anuria), an established need for renal replacement therapy, and a recognized source of sepsis that had been treated with antibiotics and surgical drainage of the septic source as required. Empirical antibiotics were administered initially and were changed as culture sensitivities indicated. Patients were excluded if they had end-stage renal failure, acquired immunodeficiency syndrome, a life expectancy less than 6 months, or if withdrawal of therapy was a possibility. All patients were receiving mechanical ventilation for respiratory failure, although this was not a criteria for inclusion. No changes to ventilatory modes were made during the study, and the only sedative agents used were morphine and midazolam, titrated to patient comfort and a Ramsay score of 4. No muscle relaxants were used.

Study design

Patients were randomized to receive either an 8-h session of isovolaemic CVVH or of isovolaemic HVHF. The order in which CVVH or HVHF were applied was random (sealed opaque envelopes). The first session was followed by an overnight wash-out period. On the second day 8 h of the alternative therapy was applied (cross-over design). Each trial session was commenced with a fresh haemofilter. Periods of 8 h were chosen because of the availability of additional nursing staff. Treatment during the run-in and wash-out periods was left to the discretion of the treating clinician and could be either CVVH at 2 l/h or no renal replacement therapy. If CVVH continued overnight, it was stopped at least 3 h before each trial session. Institutional approval was granted by the hospital Ethics Committee.

CVVH technique

Vascular access was obtained with 13.5-FG dual lumen catheters (Niagara, Bard, Ontario, Canada). A BMM 10-1 machine was used for CVVH (Gambro, Lund, Sweden) with a 1.2 m^2 AN69 polyacrylonitrile filter (Filtral 12, Hospal, Lyon, France). Blood flow was set at 200 ml/min and ultrafiltrate flow at 1 l/h. Lactate-buffered replacement fluid (Haemofiltration Replacement Fluid, Baxter Healthcare, Sydney, Australia) was delivered pre-filter at a rate controlled by volumetric pump (Gemini PC-2, IMED Corporation, San Diego, Calif., USA). Potassium chloride (13.4 mmol) was added to each 5-l bag of replacement fluid to prevent hypokalaemia.

HVHF technique

A BM 11/14 machine was used for HVHF (Baxter Healthcare) together with a 1.6 m^2 AN69 filter (Filtral 16, Hospal). Blood flow was set at 300 ml/min (to enable the desired fluid exchange), and ultrafiltrate flow at 100 ml/min. The same lactate-buffered replacement fluid (Baxter Healthcare) was used. One-third of the replacement fluid was delivered pre-filter (to avoid excessive haemoconcentration) by volumetric pump (Gemini PC-2), and two-thirds was delivered post-filter. Additional potassium and phosphate ions were added to each 5-l bag of HVHF replacement fluid

(KH_2PO_4 and K_2HPO_4: David Bull Laboratories) to prevent hypophosphataemia and hypokalaemia.

All replacement fluid was warmed for both techniques. For both techniques heparin sodium was administered pre-filter at a rate of 1000 IU/h, while protamine sulphate (Fisons Pharmaceuticals, Sydney, Australia) was administered post-filter at a rate of 10 mg/h (regional anticoagulation).

All fluid therapy not related to haemofiltration was controlled by the attending physician and recorded. Total patient fluid balance was calculated for each session. Nutritional fluids and medications were continued unchanged during each treatment.

Measurements

Mean systemic arterial pressure (MAP), right atrial pressure (RAP), pulmonary artery occlusion pressure (PAOP), cardiac index (CI) and norepinephrine dose required to maintain MAP higher than 70 mmHg were measured at baseline and hourly thereafter. The bedside nurse was instructed to maintain MAP higher than 70 mmHg by adjusting the dose of norepinephrine infusion. If the mean blood pressure was above target, the nurse was instructed to reduce norepinephrine dose by 1 μg/min and observe the patient's response. If the blood pressure remained above target for the ensuing 10 min, the nurse was instructed to lower the norepinephrine dose once again as described. If the mean arterial pressure decreased to below target and remained below target for more than 10 min, the nurse was instructed to increase the infusion rate by 1 μg/min. This procedure was the same for both therapies. Core body temperatures were recorded hourly by the pulmonary artery thermistor probe.

Blood was collected from patients at baseline and after 2, 6 and 8 h; ultrafiltrate was collected after 2, 6 and 8 h for mediator assay during each session. Blood was drawn into refrigerated tubes containing solid heparin and was immediately centrifuged at 4000 rpm for 5 min. Blood supernatant and ultrafiltrate were stored at −70°C.

Assay procedures

Activated complement fractions C3a and C5a were determined in triplicate using a commercial radioimmunoassay from Amersham (Paris, France). The respective limits of detection were 50 and 10 pg/ml, with a coefficient of variation less than 5% from 20 to 2000 pg/ml.

Interleukin (IL) 2, 6, 8 and 10 and interferon (IFN) γ concentrations were measured in duplicate by enzyme-linked immunosorbent assay according to the manufacturer's instructions (DuoSET kits, Genzyme Diagnostics, Cambridge, Mass., USA, for IL-2, IL-6, IL-8, and IFN-γ; Medgenix, Rungis, France, for IL-10). The lower limits for detection were as follows (pg/ml): IL-2, 3.0; IL-6, 10; IL-8, 3.0; IL-10, 3.0; IFN-γ, 1.0. The coefficient of variation in each assay was less than 10% for concentrations between 15.6–1000 pg/ml.

Tumour necrosis factor (TNF) α and IL-1β were measured by "sandwich" technique. Plates were coated with mouse anti-human TNF-α or IL-1β antibodies (2 μg/ml; Genzyme Diagnostics), which bound the TNF-α and IL-1β from the sample. This complex reacted with a combination of polyclonal rabbit anti-human TNF-α or IL-1β antibodies (Genzyme Diagnostics) and their swine anti-rabbit horse radish peroxidase conjugate (Dako, Carpinteria, Calif., USA). Colour development in plates due to the bound peroxidase was then read at 450 nm in a plate reader (Microplate Reader Model 550; Bio-Rad Laboratories, Hercules, Calif., USA). The lower limits of detection were 10 pg/ml. The coefficient of variation was 10% for a TNF-α concentration between 23.4 and 1500 pg/ml and for an IL-1β concentration between 15.6 and 1000 pg/ml.

Analysis of data

Data are presented as medians with interquartile range (IQR) unless otherwise stated. Baseline haemodynamic parameters were compared between HVHF and CVVH and then first treatment and second treatment by Wilcoxon rank sum. Haemodynamic variables and cytokine concentrations were analysed separately for CVVH and HVHF to identify whether changes had occurred over time (Friedman's two-way analysis of variance with post-hoc Wilcoxon signed rank test).

The area under the curve (AUC) was calculated for haemodynamic parameters and plasma cytokine concentrations using the trapezium method [15]. These were subtracted from a baseline AUC (baseline value ×8 h) to yield a ΔAUC value. Similar AUC values were also calculated for ultrafiltrate cytokine concentrations, and the percentage of the circulating cytokine load cleared by convection alone was calculated by comparing the respective AUC for plasma values and ultrafiltrate over 8 h.

The ΔAUC for haemodynamic parameters, ΔAUC for mediators, changes in norepinephrine dose, changes in body temperature and fluid balances from baseline to 8 h were compared between HVHF and CVVH using the method outlined by Hill and Armitage [34]. We used Spearman's test to check for correlations between changes in norepinephrine dose and changes in the concentration of mediators, body temperature and fluid balance. A p value less than 0.05 was considered significant.

Results

Haemodynamic effect

Baseline haemodynamic parameters (Table 2) did not differ significantly between HVHF and CVVH, or between first and second treatments.

Patients were generally recruited relatively late after the onset of septic shock [median 71 h, interquartile range (IQR) 76]. There were no sustained episodes of hypoxaemia or hypercapnia during the trial period. Two patients did not receive any additional haemofiltration during either wash-out period, and both these patients received HVHF first. All other patients received CVVH at 2 l/h before and between the study sessions, with a gap between the end of the routine CVVH and the beginning of a trial session. The median gap before the first session was 4 h (IQR 2.5), and the median gap before the second session was 5 h (IQR 4.5). Fresh filters were used only at the beginning of each session.

All patients were receiving a norepinephrine infusion at the start of each treatment with the dose ranging from 2 to 35 μg/min. Norepinephrine was the sole vasoactive agent for 9 of the 11 patients. The haemodynamic and norepinephrine data for one patient was excluded from analysis because an additional inotropic drug (mil-

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Table 2 Haemodynamic values at baseline for each patient [*CI* cardiac index (l min^{-1} m^{-2}), *MAP* mean arterial pressure (mmHg), *RAP* right atrial pressure (mmHg), *norep. dose* norepinephrine dose (μg/min), *SVR* systemic vascular resistance (dyne s^{-1} cm^{5})]

Patient no.	First therapy	Pre-HVHF						Pre-CVVH					
		CI	MAP	RAP	SVR	PAOP	Norep. dose	CI	MAP	RAP	SVR	PAOP	Norep. dose
	CVVH	3.8	81	12	552	12	32	4.0	70	11	458	14	66
2	CVVH	–	87	10	–	–	16	–	71	10	–	–	8
3	HVHF	5.7	87	10	598	10	17	3.9	74	8	744	8	18
4	HVHF	3.6	83	12	823	13	4	3.0	78	13	852	15	3
5	HVHF	3.2	87	11	950	10	40	4.5	76	9	596	9	12
6	HVHF	7.8	77	8	343	15	8	6.4	90	10	500	12	13
7	CVVH	4.3	78	13	684	12	20	5.1	76	10	580	15	35
8	CVVH	3.8	82	9	931	15	10	3.3	84	9	1034	19	6
9	CVVH	–	79	8	–	–	18	–	85	8	–	–	15
10	HVHF	3.6	79	13	765	13	18	4.2	86	17	681	16	8

rinone) was used for part of the trial period due to the onset of myocardial ischaemia (electrocardiographic changes and troponin I rise). In this patient the norepinephrine dose also fell during HVHF. One patient received additional milrinone at a constant rate during the 48-h trial period, and these haemodynamic and norepinephrine results are included.

As expected, MAP, central venous pressure (CVP), CI and PAWP did not change significantly over time during HVHF or CVVH, and MAP was maintained at target values according to instructions (Fig. 1). There was no additional effect of HVHF on the ΔAUC for MAP, CVP, CI or PAWP compared to CVVH (p values were 0.10, 0.67, 0.68, and 0.92, respectively). There was no period effect on the ΔAUC for CVP, CI or PAWP (p values were 0.73, 0.79, 0.72, respectively). However, a period effect occurred in the case of ΔAUC for MAP, with a higher average blood pressure recorded during the first session (80.4 vs. 79.4 mmHg, $p = 0.04$).

The dose of norepinephrine required for the maintenance of target MAP decreased more during HVHF than during CVVH [median 10.5 μg/min (IQR 11.0) vs. 1.0 μg/min (IQR 6.0); $p = 0.02$; proportional decrease 68% (IQR 28%) vs. 7% (IQR 59%); Fig. 2]. There was no period effect on norepinephrine dose ($p = 0.60$). The 95% confidence interval for the additional effect of a HVHF session on norepinephrine dose was a reduction of 7.6 ± 3.2 μg/min.

Body temperature fell equally during HVHF and CVVH from baseline to 8 h [median 0.9 °C (IQR 0.6°) vs. 0.7 °C (IQR 0.7)] without any additional fall attributable to HVHF ($p = 0.21$) or period effect ($p = 0.11$). There was no correlation between the decrease in temperature and the decrease in norepinephrine dose. Fluid balances during the 8-h sessions of HVHF and CVVH were positive [median 732 ml (IQR 1325) vs. 630 ml (IQR 1401)] and mostly due to the administration of nutritional fluids. There was no treatment or period effect on the fluid balance ($p = 0.14$ and $p = 0.11$, respectively) and no correlation between the fluid balance and the associated decrease in norepinephrine dose.

None of the tests for interactions between treatment and period were significant for haemodynamic parameters, norepinephrine dose, temperature or fluid balance.

Plasma concentrations of mediators

C3a, C5a, IL-2, IL-8, IL-10, and TNF-α were detected in the plasma of all patients at virtually all time points. IL-6 and IFN-γ were rarely detected, and IL-1β was not detected. The concentrations of IL-6 and IFN-γ were not analysed further.

All mediators except IL-2 showed significant changes in concentration during both therapies (C3a, C5a and IL-10) or during HVHF (IL-8 and TNF-α) according to a significant finding by Friedman's test. The most important reductions in the plasma concentration of mediators occurred between baseline and 2 h (Fig. 3). Analysis of the proportional reduction in concentrations for C3a, C5a, IL-8, IL-10 and TNF-α from baseline-2 h by the method of Hill and Armitage showed that this reduction was no greater for HVHF than CVVH (all p values were greater than 0.70). However, the ΔAUCs for C3a and C5a were significantly greater during HVHF than CVVH (p values were less than < 0.001 and 0.01, respectively). This was associated with a greater recovery of C3a and C5a concentrations after 2 h during CVVH than during HVHF. Tests for treatment-period interactions and period effects were not significant for any mediator delta AUC or proportional reduction in concentration between baseline and 2 h.

Trace amounts of C3a, C5a and IL-10 were detected in the ultrafiltrate, and only a small percentage of each was removed by convection (Table 3). IL-2 and TNF-α were not found in the ultrafiltrate, and IL-8 was detectable only at 8 h on four occasions.

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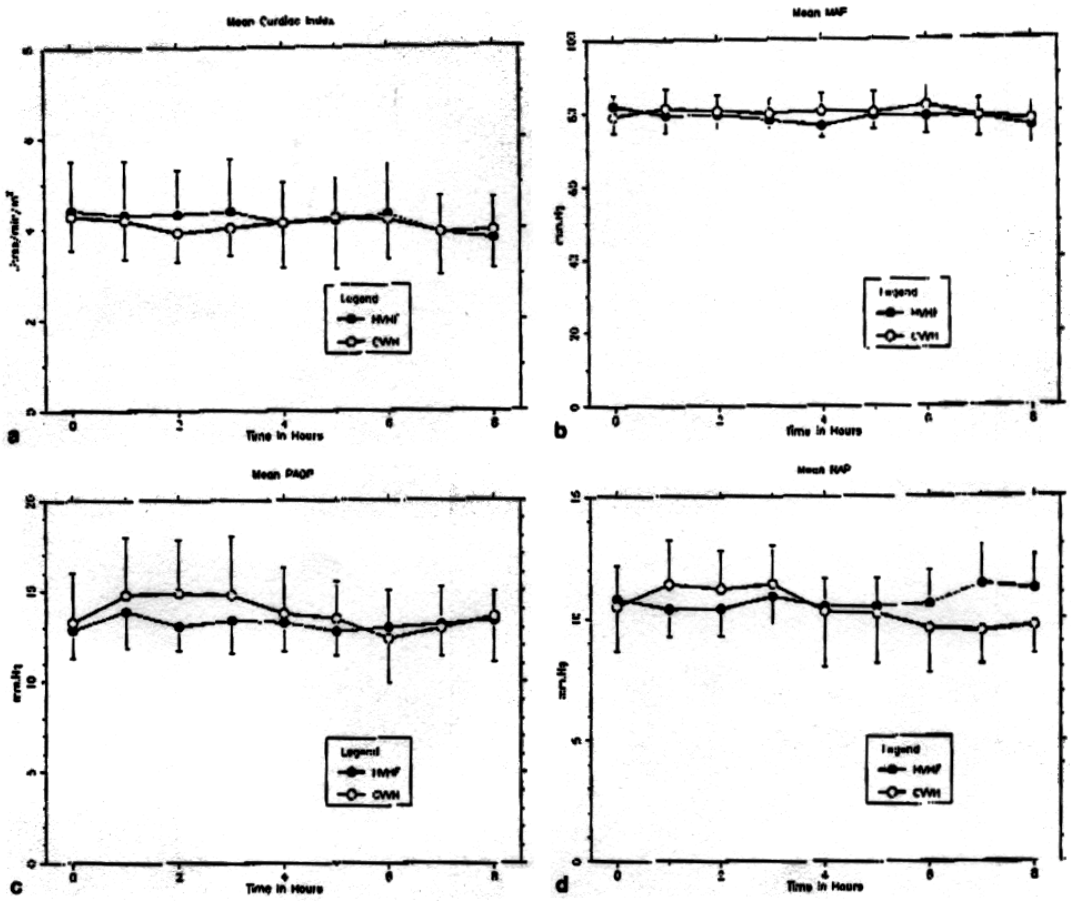

Fig. 1a–d Haemodynamic variables during HVHF and CVVH sessions. *Error bars* 95% confidence limits. a Cardiac index *(CI)*. b Mean systemic blood pressure *(MAP)*. c Pulmonary artery occlusion pressure *(PAOP)*. d Right atrial pressure *(RAP)*

No correlation was found between absolute changes in norepinephrine dose and the fall in the plasma concentration of mediators between baseline and 2 h, with the exception of C3a during CVVH ($\varrho = 0.81$, $p = 0.02$).

Discussion

The role of blood purification techniques in the management of septic shock remains controversial [16]. Recent animal experiments [12, 13, 17] and some human studies [7, 9, 18, 19, 20] suggest that continuous haemofiltration techniques lead to haemodynamic improvement. In experimental models haemodynamic changes appear most striking when treatment is "high volume" and convective [12, 14, 17, 21, 22, 23, 24, 25, 26]. These effects have been attributed to greater convective removal of soluble inflammatory mediators. We hypothesized that similar beneficial effects would be achieved in humans using high-volume haemofiltration. We also hypothesized that they would be accompanied by greater extraction of some soluble mediators of inflammation and by a decrease in their circulating blood levels. We conducted a randomized cross-over study in critically ill patients to test our hypotheses.

Some clinically relevant findings emerged from our investigation. First, it appears that HVHF can be safely performed in humans. No adverse events were noted during more than 80 h of therapy. Second, HVHF is associated with a significant decrease in vasopressor re-

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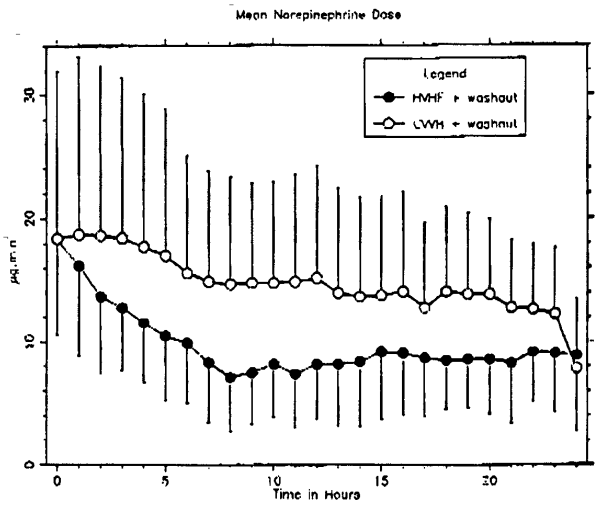

Fig. 2 Mean norepinephrine dose during HVHF and CVVH sessions including washout time (micrograms per minute). *Error bars* 95% confidence limits

quirements in human septic shock. This decrease is greater than with standard haemofiltration and is statistically and clinically significant (median decrease of 68% over 8 h). These findings are consistent with recent experimental data using similar intensity of haemofiltration [33]. To our knowledge, this is the first randomized, controlled human study to demonstrate a clinical haemodynamic benefit of a blood purification technique in human sepsis.

Several measurements were performed during the study to clarify these expected effects of HVHF. Significant decreases in the plasma levels of C3a, C5a and IL-10 were detected during both CVVH and HVHF. Such changes were most striking in the early part of the treatment session, with close to an 80% decrease in C3a, C5a and IL-10 plasma levels. Furthermore, the ΔAUC of the concentration of C3a and C5a was significantly greater during HVHF (thus resulting in decreased cumulative exposure to complement anaphylatoxins). If these effects were due to other ongoing treatments, the second session would have shown greater improvements in haemodynamics or better baseline values or lower vasopressor requirements than at the first session. However, there was no evidence for a time effect in this study.

Table 3 Percentage of convective removal of complement anaphylatoxins and cytokines. Other cytokines were only occasionally detected in the ultrafiltrate and no convective removal could be calculated

	HVHF		CVVH	
Substance		IQR		IQR

The early decrease in the plasma concentration of mediators was not explained by greater convective mediator removal during HVHF. In fact, the rapid early decline in plasma concentration strongly suggests membrane adsorption as the major mechanism for mediator removal. This observation is consistent with recent reports emphasizing the importance of cytokine removal by adsorption, and complement removal in particular [27, 28, 29, 30, 31]. HVHF should increase adsorption because of its effect on transmembrane pressure (greater membrane site recruitment) and the larger filtering membrane (greater adsorptive surface). However, adsorption may delay convective clearance because membrane saturation must occur first. If the 8-h period of therapy was insufficient for full membrane saturation to occur, this would partly explain the limited convective removal achieved. In this regard it is interesting that IL-8 was found in the ultrafiltrate only after 8 h of filtration.

The level of measured mediators may have also decreased because of adsorptive or convective removal of other "upstream" inflammatory mediators. For example, strong polyacrylonitrile membrane adsorption of complement factor D has been recently demonstrated in humans [28]. This phenomenon could then decrease C3a and C5a generation and consequently their plasma levels.

The relative reduction in C3a and C5a concentrations might explain the relatively greater reduction in

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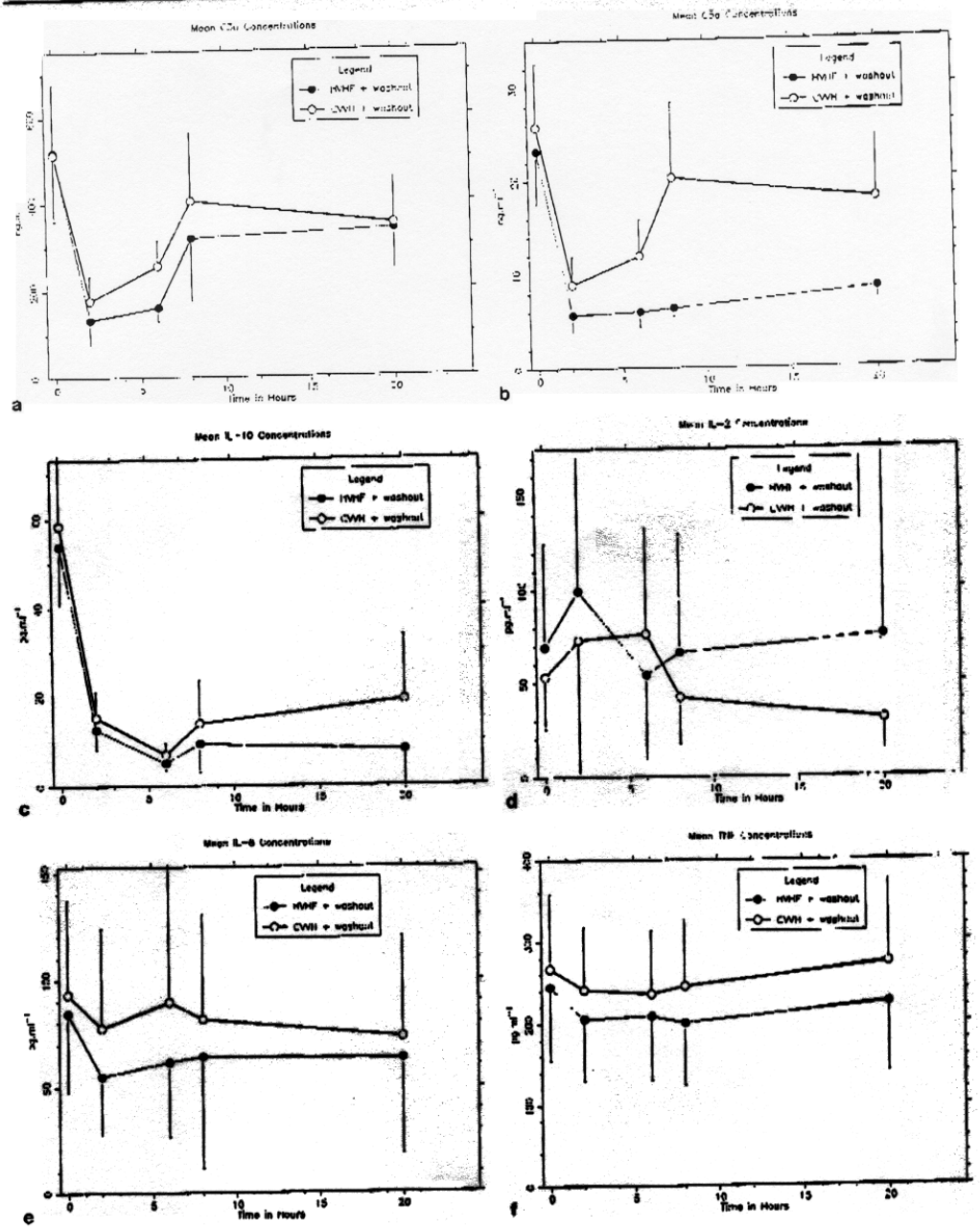

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◀ **Fig. 3a–f** Mean plasma concentrations during HVHF or CVVH sessions, including washout time. **a** C3a. **b** C5a. **c** IL-10. **d** IL-8. **e** IL-2. **f** TNF-α. *Error bars* 95% confidence limits

norepinephrine requirements during HVHF because C3a and C5a can induce vasodilatation. The maximum change in complement levels occurred in the first 2 h, and norepinephrine requirements decreased progressively during 8 h. The mechanism involved in the vascular effects of C3a and C5a would therefore have to allow alterations in tone within a few hours following changes in blood concentrations. One mechanism of complement-induced hypotension involves release of preformed histamine, which could fit in this time-frame. However, there was no simple correlation between the change in C3a and C5a and the change in vasopressor requirements.

It is also possible that unmeasured vasodilatory solutes were removed during HVHF, resulting in vasoconstriction and reduced vasopressor requirements. It is impossible to measure the plasma concentration of all known vasoactive and inflammatory solutes in sepsis. A recent animal investigation has suggested a potential effect of haemofiltration on endothelin [33].

Other mediator-independent factors measured in our study do not explain the reduction in norepinephrine dose. Fluid balance, for instance, was similar for both therapies. Haemofiltration-induced hypothermia might have been responsible for some improvement in blood pressure [32]. However, a similar decrease in body temperature occurred with both our techniques and changes in temperature was not correlated with changes in norepinephrine requirements. Similar comments apply to pH and ionized calcium. It is possible that sedative removal was more effective during HVHF, and this might have led to a greater decrease in vasopressor requirements. Only 1–3% of the total infused dose of morphine is removed by haemofiltration set at 1 l/h [35], and there are no data available for midazolam, or indeed, for any high volume technique. In our study four patients received greater amounts of sedation during their HVHF session, three received greater amounts of sedation during their CVVH session, and three received equal amounts of sedation during the two sessions.

Our study has several limitations. We did not measure several other mediators that might have helped explain our findings. The membrane used for HVHF was larger in size, thus making greater adsorption likely. However, HVHF can only be conducted with high blood flows and a membrane of sufficient size, and we wished to compare such technology to CVVH as it is currently applied in most centres. Our patients were recruited during established septic shock, and we do not know whether the same effect would be seen in during early septic shock. In this regard, a recent uncontrolled study of HVHF in early refractory shock has suggested that haemodynamic improvement is clinically significant [36]. We did not demonstrate any other beneficial effects on organ function, and such demonstration would require a phase II trial with follow-up for several days. Our investigation represents a phase I trial equivalent because we applied HVHF only for a limited period of time and cannot make comments about the immunomodulatory effects (beneficial or deleterious) of prolonged use. Finally, protective molecules or metabolites such as vitamins or amino acids might be removed during HVHF, and further investigations are necessary to establish the clinical and biochemical effects of HVHF in greater detail.

In conclusion, we have conducted the first controlled study of HVHF in human septic shock and have demonstrated a clinically and statistically significant beneficial effect of this therapy on vasopressor requirements. We have also shown that both HVHF and CVVH are associated with a temporary reduction in the plasma concentrations of several mediators of sepsis, but that HVHF is associated with a greater reduction in the concentrations of C3a and C5a. Finally, we have confirmed that removal of mediators during HVHF is likely to be adsorptive rather than convective and does not fully explain the haemodynamic effect of HVHF. We believe these findings provide a rationale to conduct further research into the effects and mechanisms of blood purification in sepsis.

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