Intensive Care Med (2008) 34:1646–1653
DOI 10.1007/s00134-008-1127-3

ORIGINAL

Nicolas Boussekey
Arnaud Chiche
Karine Faure
Patrick Devos
Benoit Guery
Thibaud d'Escrivan
Hugues Georges
Olivier Leroy

A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock

Received: 4 October 2007
Accepted: 2 April 2008
Published online: 30 April 2008

N. Boussekey (✉)
Intensive Care and Infectious Disease Unit, Tourcoing Hospital, 135, rue du Président Coty, BP 619, 59208 Tourcoing cedex, France
e-mail: nboussekey@ch-tourcoing.fr
Tel.: +33-320-694430
Fax: +33-320-694439

A. Chiche · T. d'Escrivan · H. Georges · O. Leroy
Intensive Care and Infectious Disease Unit, Tourcoing Hospital, University of Lille II, Lille, France

P. Devos
Department of Biostatistics, University of Lille II, Lille, France

K. Faure · B. Guery
Infectious Diseases Unit, CHRU Lille, University of Lille II, Lille, France

Abstract *Objective:* High volume hemofiltration (HVHF) has shown potential benefits in septic animals and a few reports suggested a hemodynamic improvement in humans. However, randomized studies are still lacking. Our goal was to evaluate the hemodynamic effects of HVHF in septic shock patients with acute renal failure (ARF). *Design and setting:* Prospective randomized study in an intensive care unit (ICU). *Patients:* Twenty patients with septic shock and ARF. *Interventions:* Patients were randomized to either high volume hemofiltration [HVHF 65 ml/(kg h)] or low volume hemofiltration [LVHF 35 ml/(kg h). Vasopressor dose was adjusted to reach a mean arterial pressure (MAP) > 65 mmHg. *Measurements and results:* We performed six hourly measurements of MAP, norepinephrine dose, PaO_2/FiO_2 and lactate, and four daily urine output and logistic organ dysfunction (LOD) score. Baseline characteristics of the two groups were comparable on randomization. Mean norepinephrine dose decreased more rapidly after 24 h of HVHF treatment compared to LVHF treatment ($P = 0.004$) whereas lactate and PaO_2/FiO_2 did not differ between the two treatment groups. During the 4-day follow-up, urine output was slightly increased in the HVHF group ($P = 0.059$) but the LOD score evolution was not different. Duration of mechanical ventilation, renal replacement therapy and ICU length of stay were also comparable. Survival on day 28 was not affected. *Conclusion:* HVHF decreased vasopressor requirement and tended to increase urine output in septic shock patients with renal failure. However, a larger trial is required to confirm our results and perhaps to show a benefit in survival.

Keywords High volume hemofiltration · Septic shock · Acute renal failure · Vasopressor · Randomized study

Introduction

Patients with acute renal failure (ARF) in intensive care unit (ICU) always have a high mortality rate ranging from 50 to 80% despite recent improvements in the management of critically ill patients [1, 2]. ARF has been shown to be an independent risk factor of mortality, particularly when patients needed renal replacement therapy (RRT) [3]. The etiology of ARF is also an important prognosis factor: septic ARF always carries increased mortality [2]. Moreover, it should be underlined that sepsis accounts for nearly half of the renal failures in ICU [2].

Recent studies established that increasing dialysis or filtration dose decreased mortality in ICU patients with ARF [4, 5]. In the last decade, several reports focused on the possible benefit of high volume hemofiltration (HVHF) in septic shock with ARF [6–11]. However, only one randomized study compared HVHF with low volume hemofiltration (LVHF) and included only ten patients [9]. At present, the question remains and recent guidelines did not recommend HVHF in the treatment of septic patients [12]. We hypothesized that HVHF could reduce vasopressor dose in patients with septic shock and ARF.

Patients and methods

This prospective randomized study was performed in the Intensive Care and Infectious Disease Unit of Tourcoing Hospital from August 2005 to January 2007. Institutional approval was granted by the regional ethics committee. Informed consent was obtained from each patient's next of kin.

Patients

Patients were eligible for recruitment if they presented septic shock and ARF with at least one of the following criteria requiring RRT [1, 13, 14]: urine output < 200 ml/12 h or anuria > 12 h, serum urea > 30 mmol/l, creatinine > 500 µmol/l or doubling of base creatinine for patients with chronic renal failure.

Patients were excluded if they suffered from obstructive or prerenal renal failure (defined by an increase in urine output and an improvement in creatinine values with adequate fluid loading), severe chronic renal failure (creatinine clearance < 30 ml/min), were included in another study, had severe immunosuppression (leukocyte count < 1,000/mm^3, >10 mg/day of prednisone or equivalent for over 2 weeks, underlying malignancy, cytotoxic drugs, radiation treatment, asplenia or AIDS) or were moribund. Exclusion was also performed if a limitation of therapy was decided, if septic shock or renal failure happened more than 5 days after ICU admission, and finally, in the absence of written consent. Patients were secondarily excluded if they died within the first day after randomization, or if the patient suffered from a disease other than septic shock.

Study goals

The primary end point was the decrease of vasopressor dose along with a stable MAP > 65 mmHg. Patients were considered to be responders to the treatment if norepinephrine dose was decreased by 75% after 24 h of hemofiltration. Secondary end points were duration of mechanical ventilation and RRT, ICU length of stay, and mortality in ICU and on day 28.

RRT procedures

Patients were randomized to receive either a 35 ml/(kg h) [4] or 65 ml/(kg h) ultrafiltrate flow. Randomization was realized by blocks: out of every four patients, two were allocated to LVHF, and two to HVHF treatment at random. Physicians and nurses were not blinded to the allocated treatment. Our study was not powered before enrolment because it was monocentric and we wanted to perform our study in a limited period (<2 years) to limit the bias related to treatment variations that could have occurred in a longer duration of time.

All patients were treated with the Prismaflex machine (Hospal, Lyon, France) using a 1.4 m^2 polyethersulfone filter (HF 1400, Hospal, Lyon, France) with a cut-off point of 20 kDa. Vascular access was obtained with dual-lumen catheters (Prismaccess, 13F, 20 cm long) inserted in the femoral or jugular vein. Blood flow was set between 180 and 250 ml/min in the LVHF group, and between 200 and 300 ml/min in the HVHF group, to reach a filtration fraction below 20%. Ultrafiltrate flow was delivered prefilter in one-third and postfilter in two-thirds of the patients. Bicarbonate-buffered replacement fluids were used for all RRT procedures. Net ultrafiltration was based on individual fluid status of the patient but to avoid substantial hypovolemia, negative fluid balance was not performed during the first day of treatment. Anticoagulation with heparin [pulse 10 IU/kg, then continuous 10 IU/(kg h)] was performed. Anticoagulation was then adjusted every 6 h according to activated partial thromboplastin time reaching to 1.5× normal. Patients with bleeding risks were treated with low-dose heparin [300 IU/(kg h)], or no anticoagulation in major risks or if they received activated protein C. At the end of the treatment, effective filtration volume (i.e., the real delivered filtration volume with regard to time to filter changes, alarms...) was recorded from the Prismaflex machine.

The protocol was driven for a maximum of 4 days or until norepinephrine was discontinued for at least 4 h with a persistent MAP > 65 mmHg. The filter was changed daily or earlier when obstructed. After the end of the protocol, 35 ml/(kg h) filtration volume was used for all the patients presenting persistent renal failure.

Septic shock management

Fluid management and vasopressor use were managed with pulse pressure variation measure [15] and echocardiography. Vasopressor dose was adjusted by physicians as long as the patients were unstable. Thereafter,

vasopressors were managed by nurses with a protocol to reach a mean arterial pressure (MAP) > 65 mmHg [16]: 0.02 γ/(kg min) increase or decrease if MAP was < or >65 mmHg, respectively. All patients were treated with intensive insulin therapy and low dose hydrocortisone. Activated protein C was prescribed in the absence of contraindication. Patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) were ventilated with low tidal volumes.

Data collection and definitions

For all the patients, the following characteristics were prospectively collected on ICU admission: age, gender, weight, indication(s) of ICU admission, severity of illness, and vital sign abnormalities.

Severity of illness was assessed by Simplify Acute Physiology Score (SAPS II) [17], Acute Physiology and Chronic Health Evaluation (Apache II) score [18], and Logistic Organ Dysfunction (LOD) score [19]. Sepsis syndrome was assessed according to the Bone's criteria [20]. Shock was defined as a sustained (≥1 h) decrease in the systolic blood pressure of at least 40 mmHg from baseline or a resultant systolic blood pressure <90 mmHg after adequate fluid replacement and in the absence of any antihypertensive drug. Antimicrobial therapy was considered appropriate when their prescription was in accordance with the infected site and adequate when no causal pathogen was resistant to the prescribed antibiotic(s).

Body weight was measured on ICU-admission with our patient-lifter. We prospectively collected, at the beginning of hemofiltration and then every 6 h during 4 days, the following variables: temperature, MAP, norepinephrine dose [γ/(kg min)], PaO_2/FiO_2, serum urea, creatinine, potassium, phosphate, lactate, and pH. Leukocyte and platelet counts, hemoglobin, urine output, LOD score, and norepinephrine daily dose were collected during the 4 days of the protocol. MAP and norepinephrine dose were also recorded during the 6 h before RRT initiation. We also recorded sepsis and ICU-related complications, duration of norepinephrine treatment, mechanical ventilation, RRT, and length of ICU stay. Mortality was recorded in ICU and on day 28. Mortality was attributed to septic shock when patients died from multiorgan failure without any possibility of vasopressor withdrawal and when no other pathologic origin could explain death.

Statistical analysis

Categorical variables were expressed in terms of frequencies. Continuous variables were expressed in mean and standard deviation when their distribution was normal. When it was not, they were expressed in median and quartiles. Comparisons between groups were performed using Fisher's exact test for categorical parameters. Continuous variables were analyzed using Wilcoxon's test. Comparisons between LVHF and HVHF groups for time-dependant variables were realized with linear mixed model. Differences between groups were considered to be significant for variables yielding a P value <0.05. Analyses were performed using SAS Software, V8.2.

Results

During the study period, 43 patients were admitted to our unit for septic shock complicated by ARF. Twenty patients were included into the study. The exclusion criteria for the remaining 23 patients were as follows: 13 patients were considered by at least two investigators to be moribund or with a decision of therapeutic limitation, four patients were already treated by chronic hemodialysis, two patients died before randomization, two patients had severe immunosuppression and finally, ARF occurred more than 5 days after ICU admission for two patients. One patient in the HVHF group was secondarily excluded because the final diagnosis was not septic shock but mesenteric ischemia.

All the patients were mechanically ventilated. Baseline characteristics of patients on randomization (H0) were not different between the two groups (Table 1). Clinical features of each patient are detailed in Table 2. Septic shock treatment was not different between the two groups (Table 3). All the patients received appropriate

Table 1 Baseline characteristics of patients on randomization

Variables	LVHF (n = 10)	HVHF (n = 9)	P
Age (years)	72.5 (54–77)	68 (58–74)	1
Male sex (n)	8	7	1
Weight (kg)	78 (71–86)	76 (70–78)	0.54
SAPS II	67 (61–75)	66 (56–69)	0.46
Apache II	33.5 (28–37)	31 (26–33)	0.9
LOD	9.5 (9–13)	9 (7–11)	0.3
Serum urea (mmol/l)	25 (18–37)	26 (17–38)	0.65
Creatinine (μmol/l)	191 (151–267)	205 (205–267)	0.39
PaO_2/FiO_2 ratio	163 (150–186)	157 (143–210)	0.71
pH	7.27 (7.23–7.35)	7.28 (7.28–7.32)	0.65
Lactate (mEq/l)	3.5 (2.3–6.6)	2.8 (2.7–3.9)	0.63
Platelet count ($10^3/mm^3$)	120 (77–197)	212 (172–232)	0.12
Temperature (°C)	36.8 (36–37.5)	37.1 (36.8–38.5)	0.16
Bacteremia (n)	3	2	1

Variables are expressed in median and quartiles

LVHF low volume hemofiltration, *HVHF* high volume hemofiltration, *LOD* logistic organ dysfunction score, *Apache* acute physiology and chronic health evaluation score, *SAPS* simplified acute physiology score

Table 2 Clinical features of studied patients

No.	Age	Gender	Apache II	Site of sepsis	Causative pathogen	HVHF	24 h-Responder status	28 day-Survival status
1	69	Male	28	Pneumonia	*L. pneumophila*	No	No	No
2	81	Male	35	Pneumonia	None	Yes	No	No
3	57	Male	35	Endocarditis	*S. aureus*	No	No	No
4	68	Male	31	Peritonitis	*E. coli*	Yes	Yes	No
5	23	Male	39	Pneumonia	*S. pneumoniae*	No	Yes	Yes
6	79	Male	21	Pyelonephritis	*P. mirabilis*	No	Yes	Yes
7	50	Male	25	Peritonitis	*B. fragilis*	Yes	Yes	Yes
8	58	Female	25	Peritonitis	None	Yes	Yes	Yes
9	77	Male	29	Pneumonia	*L. pneumophila*	No	Yes	Yes
10	44	Female	26	Meningitis	*N. meningitidis*	Yes	Yes	Yes
11	76	Male	25	Peritonitis	None	No	No	Yes
12	85	Male	30	Pyelonephritis	*P. mirabilis*	Yes	Yes	No
13	74	Male	33	Peritonitis	*E. coli*	Yes	Yes	Yes
14	54	Female	37	Bacteremia	*Streptococcus*	No	No	No
15	77	Male	38	Osteoarthritis	*S. epidermidis*	No	Yes	Yes
16	67	Male	35	Pneumonia	None	Yes	Yes	Yes
17	85	Female	32	Bacteremia	*Streptococcus*	No	No	No
18	74	Male	33	Pneumonia	None	Yes	Yes	Yes
19	41	Male	36	Pneumonia	None	No	No	No

HVHF high volume hemofiltration, *Responder status* patients are considered to be responders if norepinephrine is decreased by 75% after 24 h of hemofiltration, *Apache* acute physiology and chronic health evaluation score

Table 3 Septic shock management

Variables are expressed in median and quartiles
LVHF low volume hemofiltration, *HVHF* high volume hemofiltration, *H6s* first 6 h after the onset of septic shock, *H0r* time of randomization
H24r 24 h after randomization

Variables	LVHF ($n = 10$)	HVHF ($n = 9$)	P
Crystalloids infusion H6s (ml/kg)	12 (5–13)	21 (11–39)	0.27
Colloids infusion H6s (ml/kg)	14 (9–20)	14 (13–21)	0.93
Volume infusion H24r (ml/kg)	19 (13–32)	13 (7–33)	0.34
Time from shock to HF (h)	15.5 (9–19)	21 (19–27)	0.77
Norepinephrine requirement on H0r [γ/(kg min)]	0.5 (0.37–1.09)	1.07 (0.43–1.75)	0.35
Use of dobutamine (n)	4	3	1
Use of activated protein C (n)	2	3	0.62
Adequate antimicrobial therapy (n)	8/8	4/5	0.38

antimicrobial therapy during the first 3-h period following the onset of septic shock. Effective ultrafiltration volume was 32 ml/(h kg) in LVHF group, and 62 ml/(h kg) in HVHF group ($P < 0.001$). No adverse event associated with HVHF, like severe hypophosphatemia or hypokalaemia, was recorded.

There was a trend toward an increased dose of vasopressors in the two groups during the 6-h period prior to randomization [0.44 (0.15–0.95) γ/(kg min) 6 h before randomization vs. 0.89 (0.37–1.17) γ/(kg min) on H0 ($P = 0.056$)]. At the time of randomization, patients in the HVHF group required a higher norepinephrine dose to maintain MAP > 65 mmHg than in the LVHF group, but the difference was not significant (Table 3). After RRT initiation, MAP did not differ between the two groups and could be maintained above 65 mmHg in all patients ($P = 0.36$; Fig. 1a). In contrast, eight of the nine patients in the HVHF group responded to the treatment (decreased norepinephrine dose of more than 75% in 24 h) whereas only four of the ten patients responded in the HVHF group ($P = 0.004$; Table 4). This was particularly noteworthy during the first 6 h after HVHF initiation. Figure 2 represents the evolution of norepinephrine dose for each patient during the first day after HVHF or LVHF initiation. There was no difference in the volume infused during the 24 h after randomization. The evolution of patients treated by activated protein C was not different than the overall evolution in each group. This effect on vasopressors' requirement was, however, isolated and the other measured parameters such as lactate (Fig. 1b), PaO_2/FiO_2, and LOD score did not differ between the two groups ($P = 0.97$, 0.95, 0.96, respectively). Four patients in each group were alive with complete norepinephrine withdrawal on day 4. We noted a trend toward an increased urine output for HVHF patients between day 1 and day 4 ($P = 0.059$; Fig. 1c). Neither body temperature nor acidosis levels differed between the two groups during the study period.

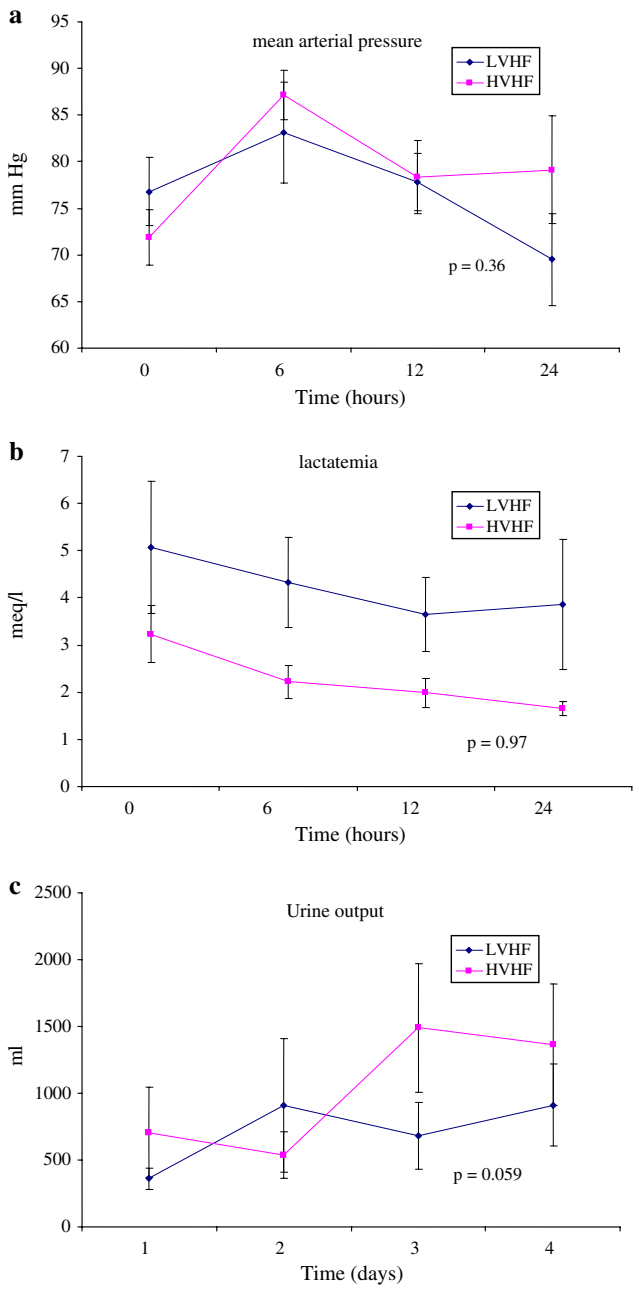

Fig. 1 Evolution during high volume hemofiltration (HVHF) and low volume hemofiltration (LVHF). **a** Mean arterial pressure, **b** lactate, **c** urine output

Sepsis and ICU-related complications were not different between LVHF and HVHF groups. Duration of mechanical ventilation [13 (6–22) days in LVHF group, 15 (7–19) days in HVHF group], of RRT [7 (2–17) vs. 6 (2–14) days], of norepinephrine requirement [2.25 (2–7) vs. 3 (2–6) days], and length of ICU stay [14.5 (7–29) vs. 18 (15–23) days] were also not different. All survivor patients had a full recovery of renal function at ICU discharge. Survival on day 28 was also not statistically different ($P = 0.65$). Six patients in the LVHF group died, five from multiorgan failure related to septic shock, and one from an anaphylactic reaction to antibiotics. In the HVHF group, only three patients died, one from the initial septic shock, the other two recovered from their sepsis and died later from tertiary peritonitis ($P = 0.11$).

Discussion

Acute renal failure is a critical event in patients with septic shock. Our study was designed to evaluate the hemodynamic effect of HVHF in these patients. The hemodynamic status was assessed through the dynamic evolution of norepinephrine dosage necessary to maintain MAP > 65 mmHg. We showed that HVHF allowed a quicker decrease in norepinephrine dose requirement and a trend to an increased urine output. In contrast, we detected no difference between the other studied parameters.

In animal studies, improvement of hemodynamic parameters with high filtration volume has been largely described for the last 15 years [21–24]. Some authors have already used HVHF as a salvage therapy in very critically ill patients. They found an increased survival in patients who showed a hemodynamic improvement with HVHF [6, 7, 10]. However, these studies included a limited number of patients and were not randomized. To date, only one randomized study was performed in cross-over and included only ten patients. The results showed a significant decrease in norepinephrine requirement during the HVHF period compared to the LVHF period [9].

Beside the observation of hemodynamic improvement with HVHF, our results bring new questions. First, we waited for RRT criteria for inclusion. The mean time elapsed between the onset of septic shock and the beginning of hemofiltration was 22 h. In all the patients we recorded a trend ($P = 0.056$) toward an increase in vasopressor requirement during the 6-h period before hemofiltration. Considering the major hemodynamic improvement, particularly during the first 6 h after HVHF initiation, it might be suggested that performing HVHF earlier in the course of septic shock could be associated with a greater benefit. In fact, experimental and human studies showed that uremic toxins have an important role in immune functions [25, 26]. Only one randomized study evaluated hemofiltration in sepsis without ARF [27]. Results were negative but a very low filtration volume was used. Moreover, Honore et al. [6], in their non-randomized study performed in refractory septic shock patients independently of renal failure, found that time to HVHF initiation was associated with survival.

Table 4 Evolution of norepinephrine dose [γ/(kg min)] with regard to the 24 h-responder status

Time (h)	LVHF		HVHF	
	Non-responders $n = 6$	Responders $n = 4$	Non-responder $n = 1$	Responders $n = 8$
0	0.99 (0.54–1.17)	0.38 (0.26–0.44)	2.38	1.01 (0.3–1.3)
6	0.94 (0.78–1.5)	0.28 (0.17–0.39)	1.19	0.45 (0.18–0.8)
12	0.81 (0.43–1.69)	0.2 (0.1–0.3)	0.95	0.27 (0.07–0.43)
18	0.73 (0.35–2.66)	0.04 (0.01–0.1)	0.83	0.19 (0.02–0.37)
24	0.56 (0.27–2.77)	0 (0–0.05)	0.95	0.06 (0–0.21)

Variables are expressed in median and quartiles
LVHF low volume hemofiltration, *HVHF* high volume hemofiltration

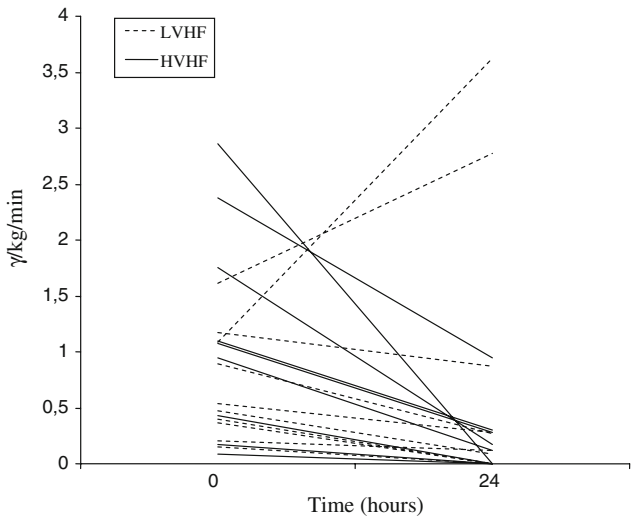

Fig. 2 Evolution of norepinephrine requirement for each patient during the first 24 h after high volume and low volume hemofiltration initiation

Patients on HVHF increased their urine output during the 4 days of the study period, but this difference was not statistically significant ($P = 0.059$), probably because of our small sample size. We can not establish a link between the rapid decrease in mean norepinephrine dose and the increase in urine output, since norepinephrine infusion have been reported to decrease renal blood flow under normal conditions [28], but had inverse effects in the case of septic shock [29]. We think that the increased urine output is probably secondary to the removal of inflammatory mediators that cause renal insult in high concentrations [14]. This result seems particularly important, since persistent oliguria is a well-known prognostic factor in the ICU.

We must underline that our study has important limitations. The major one is the small number of patients. Moreover, our study was not powered before enrolment. Then, our study was randomized, but not blinded, and was monocentric. Our method of randomization (by block) could also introduce a bias because we knew, before enrolment, the group for the last patient of each block. However, as we maintained in all patients a MAP > 65 mmHg, norepinephrine dosage was managed equally in the two groups. With regard to our inclusion criteria, RRT requirement was not defined according to the RIFLE criteria [30], but all our patients were in the renal failure class. We excluded patients who exhibited septic shock or ARF during ICU-hospitalization because of a much higher mortality rate. More than half of the patients presenting with study inclusion criteria were not included, essentially because physicians classified them as moribund or with therapeutic limitations. However, considering the particularly high severity scores of the included patients (80% predicted mortality), we think that this was not a selection bias. Another limitation of our study could be the protocol we used for vasopressors' management, which only included MAP, without any systematic measurement of other hemodynamic variables like cardiac index, systemic vascular resistance or venous oxygen saturation. Moreover, we did not measure cytokine kinetics, which might have potentially explained the hemodynamic improvement. However, our goal was to perform a clinical study with a reliable target (MAP) that can be applied in every ICU. The last limitation is the HVHF procedure. Beside the critical question about when to start hemofiltration in septic shock, other interrogations remain concerning the optimal filtration volume and the adequate duration of hemofiltration with high volume. In our study, we used 65 ml/(kg h) for logistic reasons. However, experimental and clinical studies suggest that a much higher filtration volume during limited time could offer significant hemodynamic improvement [6, 24]. Moreover, we noticed major hemodynamic improvement during the first 6 h of HVHF. It could probably be safe, time- and cost-effective to perform high volume during this short period, and continue RRT with smaller volumes, as demonstrated in the study by Ratanarat et al. [31].

In conclusion, our study shows that HVHF decreased vasopressor requirement and tended to increase urine output in septic shock patients with renal failure. We must underline that important limitations, principally our small

sample size, the unblinded design, and the sole target MAP > 65 mmHg to adapt vasopressor dosage, could restrict the results. A larger study should be realized to confirm our results and perhaps to show a benefit in sepsis-related and ICU-related mortality.

Acknowledgments Tourcoing hospital provided the financial support for this study.

Conflict of Interest The authors have no financial involvement with any organization or entity with a financial interest in the subject discussed in the manuscript.

References

1. Murray P, Hall J (2000) Renal replacement therapy for acute renal failure. Am J Respir Crit Care Med 162:777–881
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
3. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30:2051–2058
4. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G (2000) Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 356:26–30
5. Schiffl H, Lang SM, Fischer R (2002) Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346:305–310
6. Honore PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, Hanique G, Matson JR (2000) Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 28:3581–3587
7. Joannes-Boyau O, Rapaport S, Bazin R, Fleureau C, Janvier G (2004) Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. ASAIO J 50:102–109
8. Oudemans-Van Straaten HM, Bosman RJ, van der Spoel JI, Zandstra DF (1999) Outcome of critically ill patients treated with intermittent high-volume hemofiltration: a prospective cohort analysis. Intensive Care Med 25:814–821
9. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P (2001) High-volume hemofiltration in human septic shock. Intensive Care Med 27:978–986
10. Cornejo R, Downey P, Castro C, Romero C, Regueira T, Vega J, Castillo N, Andresen M, Dougnac A, Bugedo G, Hernandez G (2006) High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 32:713–722
11. Piccinni P, Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, Zamperetti N, Brendolan A, D'Intini V, Tetta C, Bellomo R, Ronco C (2006) Early isovolaemic hemofiltration in oliguric patients with septic shock. Intensive Care Med 32:80–86
12. Cariou A, Vinsonneau C, Dhainaut JF (2004) Adjunctive therapies in sepsis: an evidence-based review. Crit Care Med 32:S562–S570
13. Bellomo R, Ronco C (1998) Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int 66:S106–S109
14. Lameire N, Van Biesen W, Vanholder R (2005) Acute renal failure. Lancet 365:417–430
15. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
16. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL (2008) Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. Intensive Care Med 34:17–60
17. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
18. Larvin M, McMahon MJ (1989) APACHE-II score for assessment and monitoring of acute pancreatitis. Lancet 2:201–205
19. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D (1996) The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 276:802–810
20. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1989) Sepsis syndrome: a valid clinical entity. Methylprednisolone Severe Sepsis Study Group. Crit Care Med 17:389–393
21. Stein B, Pfenninger E, Grunert A, Schmitz JE, Hudde M (1990) Influence of continuous haemofiltration on haemodynamics and central blood volume in experimental endotoxic shock. Intensive Care Med 16:494–499
22. Gomez A, Wang R, Unruh H, Light RB, Bose D, Chau T, Correa E, Mink S (1990) Hemofiltration reverses left ventricular dysfunction during sepsis in dogs. Anesthesiology 73:671–685
23. Bellomo R, Kellum JA, Gandhi CR, Pinsky MR, Ondulik B (2000) The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. Am J Respir Crit Care Med 161:1429–1436
24. Grootendorst AF, van Bommel EF, van der Hoven B, van Leengoed LA, van Osta AL (1992) High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. Intensive Care Med 18:235–240
25. Martin-Malo A, Carracedo J, Ramirez R, Rodriguez-Benot A, Soriano S, Rodriguez M, Aljama P (2000) Effect of uremia and dialysis modality on mononuclear cell apoptosis. J Am Soc Nephrol 11:936–942
26. Haag-Weber M, Horl WH (1993) Uremia and infection: mechanisms of impaired cellular host defense. Nephron 63:125–131
27. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C (2002) A phase II randomized, controlled trial of continuous hemofiltration in sepsis. Crit Care Med 30:100–106

28. Bellomo R, Ronco C (2001) The renal effets of noradrenaline and dopamine. Contrib Nephrol 132:146–157
29. Di Giantomasso D, Morimatsu H, May C, Bellomo R (2003) Intrarenal blood flow distribution in hyperdynamic septic shock: effects of norepinephrine. Crit Care Med 31:2509–2513
30. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, the ADQI workgroup (2004) Acute renal failure—definition, outcome measures, animal models, fluid therapy and information needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8:R204–R212
31. Ratanarat R, Brendolan A, Piccinni P, Dan M, Salvatory G, Ricci Z, Ronco C (2005) Pulse high-volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival. Crit Care 9:294–302