Intensive Care Med
DOI 10.1007/s00134-006-0118-5

ORIGINAL

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High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock

Received: 28 January 2005
Accepted: 15 February 2006

Electronic supplementary material
The electronic reference of this article is http://dx.doi.org/10.1007/s00134-006-0118-5. The online full-text version of this article includes electronic supplementary material. This material is available to authorised users and can be accessed by means of the ESM button beneath the abstract or in the structured full-text article. To cite or link to this article you can use the above reference.

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Abstract *Objectives:* To evaluate the effect of short-term (12-h) high-volume hemofiltration (HVHF) in reversing progressive refractory hypotension and hypoperfusion in patients with severe hyperdynamic septic shock. To evaluate feasibility and tolerance and to compare observed vs. expected hospital mortality. *Design and setting:* Prospective, interventional, nonrandomized study in the surgical-medical intensive care unit of an academic tertiary center. *Patients:* Twenty patients with severe septic shock, previously unresponsive to a multi-intervention approach within a goal-directed, norepinephrine-based algorithm, with increasing norepinephrine (NE) requirements ($> 0.3\ \mu g\ kg^{-1}\ min^{-1}$) and lactic acidosis. *Interventions:* Single session of 12-h HVHF. *Measurements and results:* We measured changes in NE requirements and perfusion parameters every 4 h during HVHF and 6 h thereafter. Eleven patients showed decreased NE requirements and lactate levels (responders). Nine patients did not fulfill these criteria (nonresponders). The NE dose, lactate levels, and heart rates decreased and arterial pH increased significantly in responders. Hospital mortality (40%) was significantly lower than predicted (60%): 67% (6/9) in nonresponders vs. 18% (2/11) in responders. Of 12 survivors 7 required only a single 12-h HVHF session. On logistic regression analysis the only statistically significant predictor of survival was the response to HVHF (odds ratio 9). *Conclusions:* A single session of HVHF as salvage therapy in the setting of a goal-directed hemodynamic management algorithm may be beneficial in severe refractory hyperdynamic septic-shock patients. This approach may improve hemodynamics and perfusion parameters, acid-base status, and ultimately hospital survival. Moreover, it is feasible, and safe.

Keywords Septic shock · High-volume hemofiltration · Algorithm · norepinephrine

Introduction

Septic shock is highly lethal [1]. Some novel therapies have demonstrated a positive effect on mortality [2], and others that appear biologically rational, such as hemofiltration methods, also have been tested [3]. Early septic shock mortality is predominantly the result of refractory hypotension [4]. High-volume hemofiltration (HVHF) may remove proinflammatory mediators involved in the hemodynamic collapse [5]. In the 1990s the value of HVHF in experimental hypodynamic septic shock was demonstrated [6]. In clinical setting several studies focused mainly on hypodynamic septic-shock patients with renal failure, demonstrated hemodynamic improvement also [7]. Nevertheless, the most prevalent condition is hyperdynamic septic shock [8], but there are no studies in this setting [5].

In our study we applied HVHF as the final step (salvage therapy) of a sequential, goal-directed protocol that includes current recommendations for the management of patients with hyperdynamic septic shock [9]. Our hypothesis was that HVHF improves hemodynamics and perfusion in patients with progressive refractory hypotension and lactic acidosis. We evaluated the effect of short-term HVHF (12-h period) on norepinephrine (NE) requirements and arterial lactate. Secondary objectives were to evaluate feasibility, tolerance, and potentially serious adverse events (SAEs) of HVHF and to compare observed vs. expected hospital mortality.

Materials and methods

Study population

This was a prospective, interventional, nonrandomized clinical study conducted at the surgical-medical intensive care unit of the Catholic University of Chile Hospital between November 2002 and September 2004. It was approved by the institutional ethics committee. All patients or their relatives signed an informed consent.

We included 20 consecutive patients with hyperdynamic septic shock (cardiac index, CI, $> 3\,\mathrm{l\,min^{-1}\,m^{-2}}$) [10] refractory to all preceding treatments according to our management algorithm (Fig. 1) and who had both increasing NE requirements ($> 0.3\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$) and worsening lactic acidosis. Patients undergoing previously determined conservative management or experiencing active bleeding or an undrained source of surgical sepsis, and/or who were over 85 years of age were excluded. Severity of illness and predicted mortality were assessed in all patients using the Acute Physiology and Chronic Health Evaluation (APACHE II) [11] and the Sequential Organ Failure Assessment (SOFA) score [12] was recorded daily (Table 1). The first short-term HVHF started within 6 h of reaching NE threshold. Patients' mean age was 52.5 ± 18.5 years, with a mean APACHE II of 26.1 ± 3.1 and mean SOFA scores of 13 ± 3. Abdominal infection was the cause of septic shock in seven patients (35%), pulmonary infections in six (30%), urosepsis in three (15%), and various other causes were found in the four remaining (20%; Table 1)

Hemodynamic and metabolic variables

We measured core body temperature (T°), heart rate (HR), mean arterial pressure (MAP), NE requirements, lactate, mixed venous oxygen saturation (S_vO_2), and pulmonary artery catheter-derived hemodynamic variables (CI; pulmonary arterial occlusion pressure, PAOP; central venous pressure, CVP; systemic vascular resistance index, SVRI) at baseline (t_0) and every 4 h (t_4, t_8, t_{12}) during a 12-h period of HVHF and every 6 h thereafter (t_{18}, t_{24}). t_{18} and t_{24} measurements were aimed at detecting rebound effect after HVHF and we actively looked for potential SAEs. ICU and hospital length of stay and mortality were recorded. All patients had an arterial line and a pulmonary artery catheter in place; six of these had the CCO/SvO_2/CEDV catheter (Vigilance 2 Monitor, Edwards Lifesciences Irvine, Calif., USA). Intra-abdominal pressure (IAP) was measured every 6 h by the modified Kron technique [13]. Intra-abdominal hypertension (IAH) was diagnosed and classified according to WSACS consensus [14].

Management algorithm

To manage septic-shock patients we used a multi-intervention approach within an NE-based algorithm [15]. This incorporates new evidence-based pharmacological therapies and recommendations [9, 16] and commands various subsequent interventions according to NE requirements (Fig. 1) aimed at maintaining MAP higher than 70 mmHg and normal perfusion parameters (lactate, S_vO_2) [2]. Sequential steps starting with fluids were undertaken each time that MAP fell below 70 mmHg. Preload optimization was obtained using a fluid bolus and PAOP/CI measurements to generate a Starling curve. Colloids were used for fluid challenge, and optimal PAOP was defined as the level at which CI increased less than 10% between measurements. A nurse adjusted NE infusion rate every hour to the minimal dose necessary to maintain the MAP goal. PAOP was also reevaluated every hour, adjusting fluids to the optimal level (see above).

Low-dose steroids are used for patients requiring more than $0.1\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$ NE (adapted from the criteria of Annane et al. [17]). DrotAA is indicated for patients with fulminant disease reaching the NE threshold of more than $0.3\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$ in less than 12 h and without contraindications (from Laterre and Wittebole's [18] early entry

Table 1 Characteristics at baseline of 20 patients with hyperdynamic septic shock treated with a single 12-h session of high-volume hemofiltration (HVHF) (*A. fumigatus Aspergillus fumigatus*, *E. cloacae Enterobacter cloacae*, *N. meningitidis Neisseria meningitidis*, *P. aeruginosa Pseudomona aeruginosa*, *S. group A Streptococcus* group A, *S. pneumoniae Streptococcus pneumoniae*, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *ARDS* acute respiratory distress syndrome, *BSA* body surface area, *CNS* central nervous system, *delay* time between onset of shock or to the moment at which severity threshold was reached and the start of HVHF, *HD* hemodialysis, *HVHF* high-volume hemofiltration, *IAP* intra-abdominal pressure, *MODS* multiple organ dysfunction syndrome, *response* defined by attaining hemodynamic and metabolic goals at the end of 12 h of HVHF, *MRSA* methicillin-resistant *Staphylococcus aureus*, *SLE* systemic lupus erythematosus, *SOFA* Sequential Organ Failure Assessment, *survival* hospital survival)

Case no.	Age (years)	Gender	Disease	Bacteria	Initial antibiotic therapy	APACHE II	SOFA	BSA	IAP (mmHg)	HVHF (*n*)	Delay (h)	HD (*n*)	Response	Survival
1	31	M	Pneumonia, ARDS	*E. cloacae* *A. fumigatus*	Cefotaxime + metronidazole[a]	25	14	1.83	12	4	6	0	Yes	Yes
2	68	M	ARDS, acute renal failure	Hantavirus	Cefotaxime + metronidazole[a]	29	13	1.96	11	2	4	7	Yes	Yes
3	41	F	Pneumonia, ARDS, chronic myeloid leukemia	*S. pneumoniae*	Imipenem + vancomicyn	27	17	1.60	17	3	6	0	No[c]	Yes
4	61	F	Urosepsis, acute renal failure, breast cancer	*Escherichia coli*	Cefotaxime	28	18	2.02	10	1	3	8	Yes	Yes
5	16	F	Pancreatitis, acute lymphoblastic leukemia	*Escherichia coli*	Imipenem + vancomicyn	24	12	2.00	18	3	3	0	Yes	Yes
6[b]	59	M	Bowel obstruction, coronary heart disease	*Escherichia coli*	Cefotaxime + metronidazole	21	10	2.01	21	3	5	0	Yes	Yes
7	61	M	Urosepsis, uretheral lithiasis	*Escherichia coli*	Cefotaxime	28	12	2.17	15	1	2	0	No[c]	Yes
8	37	M	Streptococcal toxic shock, pneumonia	S. group A	Penicillin + clyndamicim	24	11	2.04	13	1	2	4	No[c]	Yes
9	43	F	Orbitary mucormycosis, Pancytopenia	*Zygomycetes* spp	Ceftazidime + amikacin[a]	24	13	1.89	9	1	5	6	Yes	Yes
10[b]	74	F	Colonic perforation	*Escherichia coli*	Cefotaxime + metronidazole	28	6	1.97	21	1	5	7	Yes	Yes
11	77	M	Pneumonia, ARDS, retroperitoneal hematoma	*P. aeruginosa*	Cefotaxime + metronidazole[a]	30	10	2.07	16	1	2	0	Yes	Yes
12	54	M	Pneumonia, systemic candidiasis	*Candida albicans*	Cefotaxime + metronidazole	29	13	1.81	11	1	5	0	Yes	Yes
13	17	M	Febrile neutropenia, non-Hodgkin lymphoma	MRSA	Imipenem + vancomicin	29	17	1.92	16	2	4	0	No	No
14	37	F	Meningococcemia, SLE	*N. meningitidis*	Ceftriaxone	28	15	1.99	16	4	6	0	No	No
15	59	F	Mesenteric ischemia, pneumonia	*K. pneumoniae*	Cefotaxime + metronidazole[a]	25	15	1.87	16	2	2	0	No	No
16[b]	75	M	Acute cholecystitis, pancreatitis, ARDS	All cultures negatives	Cefotaxime + metronidazole	26	9	2.07	16	1	4	6	No	No
17[b]	49	F	Bariatric surgery, urosepsis, ARDS	All cultures negatives	Piperacillin, tazobactam	26	13	1.83	14	1	5	0	No	No
18	61	M	Peumonia, ARDS, chronic liver failure	*Enterococcus* spp	Cefotaxime + metronidazole[a]	27	14	1.94	12	1	4	0	No	No
19[b]	77	M	Acute cholecystitis	*E. coli*, *Enterococcus* spp	Cefotaxime + metronidazole[a]	27	13	1.89	23	2	3	4	Yes	No[d]
20[b]	53	M	Acute cholecystitis, pancreatitis, MODS	All cultures negatives	Cefotaxime + metronidazole	17	14	2.20	24	4	2	10	Yes	No[d]

[a] Initial empiric antibiotic therapy had to be changed according to bacteriology [b] Postoperative patient. [c] Patient attained responder criteria after first HVHF [d] Late death by gastrointestinal bleeding

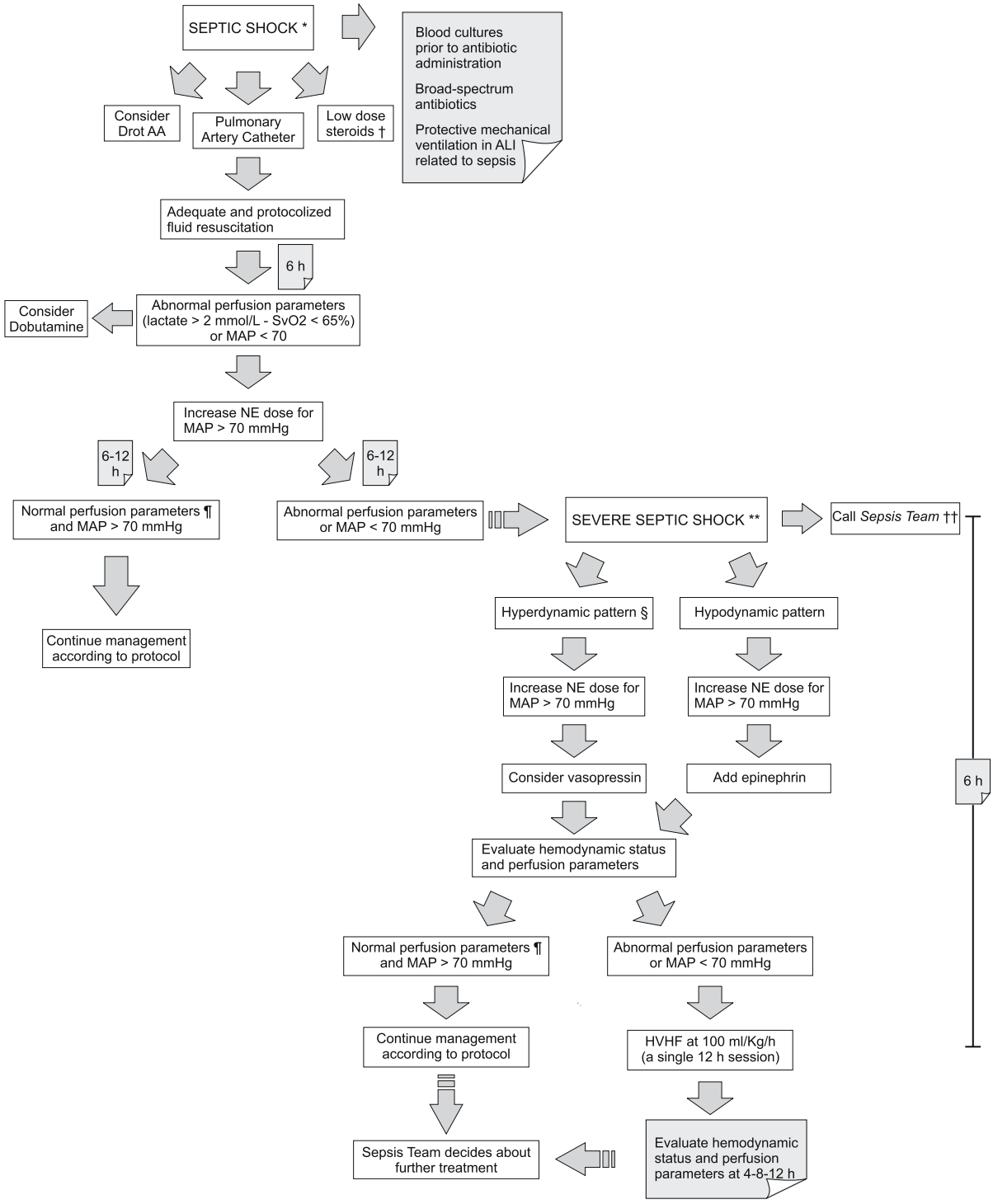

Fig. 1 Evidence-based management algorithm for septic shock. *DrotAA* Activated protein C; *MAP* mean arterial pressure; *NE* norepinephrine; *HVHF* high-volume hemofiltration. * Sepsis induced hypotension unresponsive to an adequate fluid resuscitation *and* requiring less than $0.3\,\mu g\,kg^{-1}\,min^{-1}$ NE for MAP > 70 mmHg. ** Sepsis-induced hypotension unresponsive to an adequate fluid resuscitation *and* requiring more than $0.3\,\mu g\,kg^{-1}\,min^{-1}$ NE for MAP > 70 mmHg. † In patients requiring $> 0.1\ \mu g\,kg^{-1}\,min^{-1}$ of NE for MAP > 70 mmHg. †† ICU staff and residents, plus dedicated infectologist, nephrologist, surgeon, and radiologist. § Cardiac index $> 3.0\,l\,min^{-1}\,m^{-2}$. ¶ $S_vO_2 > 65\%$ and lactate level < 2 mmol/l

criteria). Dobutamine and epinephrine are reserved for hypodynamic patients. Vasopressin is administered to severe hyperdynamic patients (with NE requirements greater than $0.3\,\mu g\,kg^{-1}\,min^{-1}$ and CI greater than 3.0 l/min) at a fixed dose of 0.02 U/min in an effort to reduce NE doses. A multidisciplinary team ("sepsis team") made fundamental decisions (Fig. 1), and initial empirical antibiotic therapy was adjusted later according to cultures and antimicrobial sensitivity.

All patients received steroids (hydrocortisone 300 mg/day). Nine patients fulfilled criteria for DrotAA but only four (two responders) received the drug; there were contraindications in the other five. No patient received dobutamine or epinephrine. Vasopressin was available only for the last eight patients in our series (four in each group) and was used in an unsuccessful effort to decrease NE levels in the 6 h previous to HVHF (Table 1, Fig. 1). All patients were on mechanical ventilation and managed according to current recommendations [19]. Sedation was titrated to a Sedation-Agitation Scale score of 4 or 5 [20].

Hemofiltration technique

A double-lumen 11-F catheter (Vas-cath, Bard, Utah, USA) was inserted percutaneously in the femoral or internal jugular vein. Hemofiltration was performed with a polysulfone hemofilter, $1.33\,m^2$ surface area, 220-μm pore size, and priming volume of 90 ml (Ultraflux AV 600, Fresenius Medical Care, Germany). The hemofiltration monitor was set to deliver 200 ml/min blood flow and an ultrafiltration rate of $100\,ml\,kg^{-1}\,h^{-1}$ (Diapact, BBraun, Germany). Ultrafiltration rate was increased gradually over 60–120 min according to hemodynamic tolerance to reach the target rate. A neutral fluid balance was programmed. Blood ultrafiltrate was replaced using a bicarbonate-based solution with the following composition: sodium 140 mEq/l potassium 2.0 mEq/l, calcium 1.5 mEq/l, magnesium 0.5 mEq/l, chloride 111 mEq/l, bicarbonate 35 mEq/l, glucose 1 g/l, and osmolality 296 mOsm/kg (BBraun). Body temperature was kept over 35°C using a heating device supplied with the monitor. No anticoagulation was used. Blood lines were flushed every 30 min with 150 ml of a 0.9% NaCl solution to check for permeability.

All patients received at least one short-term (12-h) period of HVHF with a single hemofilter. Thereafter individual response was evaluated by the sepsis team, and additional hemofiltration procedures were decided on, as needed. Only the first 12-h period is reported here. HVHF was started in all patients within 6 h of reaching the severity threshold with no significant differences between the two groups in delay time (Table 1). When analyzing delay between onset of septic shock and HVHF, no significant difference between responders and nonresponders was observed: 24 ± 11 h vs. 21 ± 17 h, respectively.

Tolerance and SAEs

The procedure was considered to be well tolerated if the 12-h session could be completed without SAEs. HVHF-related SAEs included: abrupt and life-threatening decrease in MAP during the first 30 min of the procedure or new onset of atrial fibrillation, ventricular tachycardia, or myocardial ischemia during the HVHF session.

Response to therapy

Patients were considered *responders* if at the end of the 12-h HVHF period they stabilized MAP with a $\geq 30\%$ decrease or more in both NE requirements and lactate. Otherwise they were considered *nonresponders*. Response was observed in 55% (11/20). No significant differences between responders and nonresponders were identified at baseline (Table 2).

Data analysis

Univariate analysis of variance for repeated measures was used to test for differences in continuous variables at baseline, t_4, t_8, and t_{12} in the responder and nonresponder groups. To evaluate rebound of shock during the next 12 h a new analysis of variance was carried out for the same variables at t_{18} and t_{24}. Post hoc analysis with Bonferroni's correction was used. Mixed models were adjusted to compare the course between groups. Expected (SOFA, APACHE II) and observed mortality rates were compared by Fisher's exact test. Baseline values were compared between responders and nonresponders by the nonparametric Mann-Whitney rank sum test. Multiple logistic regression was used to determine predictors of response and mortality at baseline with SIGMA STAT 3.11 (Systat Software, Richmond, Calif., USA), and SPSS 13.0 (Chicago, Ill., USA) statistical software was used. Results are expressed as mean ± SD, and differences at the level of $p < 0.05$ are considered significant.

Results

NE dose, lactate levels, and HR decreased, and arterial pH increased, all significantly only in responders during the HVHF session (Fig. 2). At 72 h only one patient still required NE infusion ($0.1\,\mu g\,kg^{-1}\,min^{-1}$). Conversely, at the same time four nonresponder patients had died from refractory shock, and three still required

Table 2 Baseline demographic and physiological values with regard to response and survival (*APACHE II* Acute Physiology and Chronic Health Evaluation II, *APTT* activated partial thromboplastin time, *BSA* body surface area, *BUN* blood urea nitrogen, *CI* cardiac index, *CVP* central venous pressure, *delay time* time between onset of shock or to the moment at which severity threshold was reached and the start of HVHF, *HVHF* high-volume hemofiltration, *HR* heart rate, *IAP* intra-abdominal pressure, *LVSWI* left ventricular stroke work index, *PAOP* pulmonary arterial occlusion pressure, *MAP* mean arterial pressure, *NE* norepinephrine, S_vO_2 mixed venous blood saturation, *SOFA S*equential Organ Failure Assessment, *SVRI* systemic vascular resistance indexed)

	Responders vs. nonresponders			Survivors vs. nonsurvivors		
	Responders ($n = 11$)	Nonresponders ($n = 9$)	p[a]	Survivors ($n = 12$)	Nonsurvivors ($n = 8$)	p[a]
Age (years)	55.7 ± 19.5	48.6 ± 17.5	0.40	51.8 ± 18.5	53.5 ± 19.7	0.85
APACHE II score	25.6 ± 4.0	26.7 ± 1.6	0.47	26.4 ± 2.8	25.6 ± 3.7	0.59
SOFA score	12.4 ± 3.0	13.7 ± 2.7	0.32	12.4 ± 3.2	13.8 ± 2.3	0.32
Body Surface Area (BSA)	2.0 ± 0.1	1.9 ± 0.2	0.62	2.0 ± 0.2	2.0 ± 0.1	0.80
HR (beats/min)	111 ± 18	121 ± 28	0.33	113 ± 20	119 ± 27	0.60
MAP (mmHg)	71.8 ± 8.7	72.8 ± 14.1	0.85	71.5 ± 12.3	73.4 ± 9.8	0.72
CI ($\mathrm{l\,min^{-1}\,m^{-2}}$)	4.0 ± 0.9	5.3 ± 1.6	0.16	4.8 ± 1.6	4.8 ± 0.8	0.91
PAOP (mmHg)	18.3 ± 5.0	18.2 ± 4.2	0.98	18.8 ± 5.1	17.4 ± 3.9	0.50
CVP (mmHg)	12.2 ± 4.0	13.1 ± 3.2	0.81	13.4 ± 3.0	13.0 ± 3.0	0.86
SVRI ($\mathrm{dyne \cdot s\,cm^{-5}\,m^{-2}}$)	1058 ± 346	917 ± 268	0.28	996 ± 399	972 ± 143	0.87
LVSWI ($\mathrm{g\,min^{-1}\,m^{-2}}$)	27.9 ± 6.9	28.0 ± 8.9	0.99	26.4 ± 7.5	30.4 ± 7.7	0.26
NE requirement ($\mu\mathrm{g\,kg^{-1}\,min^{-1}}$)	0.7 ± 0.5	0.8 ± 0.5	0.56	0.7 ± 0.4	0.8 ± 0.5	0.44
NE max.	0.8 ± 0.6	0.9 ± 0.4	0.15	0.8 ± 0.5	0.9 ± 0.5	0.14
Arterial pH	7.2 ± 0.3	7.2 ± 0.1	0.91	7.2 ± 0.3	7.2 ± 0.1	0.91
S_vO_2 (%)	72.0 ± 8.4	73.1 ± 9.8	0.79	71.6 ± 8.1	74.1 ± 8.1	0.78
Serum lactate (mmol/l)	5.7 ± 3.4	5.6 ± 2.7	0.93	5.4 ± 2.3	6.1 ± 3.9	0.91
Temperature (°C)	37.2 ± 1.0	38.2 ± 0.9	0.42	37.5 ± 1.1	37.8 ± 1.2	0.57
Creatinine (mg/dl)	3.7 ± 3.0	3.0 ± 2.6	0.59	2.9 ± 1.6	4.2 ± 4.0	0.33
Blood urea nitrogen (mg/dl)	74.6 ± 40.2	52.2 ± 27.6	0.17	62.1 ± 32.2	68.1 ± 43.0	0.72
Diuresis (ml/h)	25.9 ± 18.2	23.1 ± 23.5	0.77	24.8 ± 19.8	24.4 ± 22.4	0.96
Bilirrubin (mg/dl)	2.4 ± 2.0	3.7 ± 3.4	0.31	1.8 ± 1.1	3.1 ± 3.2	0.19
APTT (s)	46.0 ± 27.2	48.7 ± 16.6	0.80	40.0 ± 11.0	57.9 ± 31.2	0.41
Platelets (1,000/ml)	96.0 ± 72.0	77.0 ± 52.0	0.25	83.5 ± 65.4	99.5 ± 84.9	0.10
IAP (mmHg)	16.0 ± 5.6	15.0 ± 1.7	0.67	14.5 ± 4.2	17.1 ± 4.2	0.56
Delay time (h)	4.0 ± 1.7	3.9 ± 1.4	0.55	4.3 ± 1.6	3.4 ± 1.3	0.43
HVHF dose (l)	92.8 ± 8.4	90.4 ± 11.1	0.66	92.2 ± 10.4	91.1 ± 8.6	0.71

[a] Mann-Whitney nonparametric rank test

NE (0.18–0.29 $\mu\mathrm{g\,kg^{-1}\,min^{-1}}$). Nine patients (45%) had grade I IAH (IAP 12–15 mmHg), seven (35%) grade II IAH (IAP 16–20 mmHg), and four (20%) abdominal compartment syndrome (defined as IAP > 20 mmHg with new onset organ failure). There was no statistically significant difference in mortality between these subgroups.

Overall observed mortality was lower than predicted by APACHE II (40% vs. 63%, $p < 0.03$): 67% (6/9) in nonresponders vs. 18% (2/11) in responders ($p < 0.001$). Death from refractory shock occurred in four patients before 48 h, all in nonresponder group. Two responders vs. six nonresponders died during the hospitalization period ($p < 0.01$; Fig. 2). With regards to mortality, delay in start HVHF did not predict outcome either in univariate or in multivariate analyses.

In the overall series ten patients received additional HVHF sessions after the sepsis team evaluation, and eight were switched to hemodialysis according to renal supportive criteria [21] when hemodynamic parameters were stable (Fig. 1, Table 1). Of 12 survivors 7 required only a single 12-h HVHF session (Fig. 3). HVHF was well tolerated, and it could be implemented in all 20 patients within a 6-h period and none experienced SAEs.

Discussion

To our knowledge, this is the first clinical study using HVHF as salvage therapy in severe hyperdynamic septic-shock patients. The findings confirm that HVHF significantly stabilizes hemodynamics, decreases NE requirements, and improves lactate in this setting, as previously reported in hypodynamic patients [22].

We can only speculate about the mechanism. Circulating pro- and anti-inflammatory mediators are of pivotal importance in the pathogenesis of septic shock [23] and HVHF apparently improves cardiocirculatory function by removing them [24]. The "peak concentration" hypothesis suggests nonspecific removal of pro- or anti-inflammatory soluble mediators, attenuating or modulating their effects [24]. HVHF clearly induced shock reversal and lactate normalization in 55% of our patients, all of whom were previously refractory to protocol-guided, goal-directed, septic-shock management. These patients, receiving high NE doses (mean 0.75 $\mu\mathrm{g\,kg^{-1}\,min^{-1}}$), responded sometimes dramatically with an abrupt decrease in NE requirements and a progressive resolution of lactic acidosis. More important, this effect was sustained at least

12 h after a single HVHF session without rebound effect. The effect of HVHF on hemodynamics may not be explained by a positive volume balance during the procedure as HVHF was isovolemic, and PAOP remained stable. The decrease in lactate appears to be explained by a real improvement in perfusion; HVHF does not clear lactate [25] and pH increased simultaneously (see Electronic Supplementary Material, S.T1). Oxygen venous saturation was more than 70% at baseline, as is usual in hyperdynamic septic shock, and did not change significantly during the procedure. The role of temperature changes during HVHF is not clear [5]. A cooling effect may improve hemodynamics and tolerance, but we observed no significant difference in temperature between subgroups (Fig. 2).

Ultrafiltration rates and efficacy

Grootendorst et al. [26] and Rogiers et al. [27] showed improvement in hemodynamic and oxygenation parameters in experimental septic shock, with HVHF at 150 to 200 ml kg^{-1} h^{-1}. Ronco et al. [21] demonstrated that increasing ultrafiltration rates from 20 to 35 or 45 ml kg^{-1} h^{-1} improve survival in septic patients. Cole et al. [28] in a cross-over study compared an 8-h HVHF period (6 l/h; approx. 85 ml kg^{-1} h^{-1} for a 70-kg patient) and a conventional rate (2 l/h) in human septic shock and showed a statistically significant beneficial effect in reducing vasopressor requirements. Honore et al. [22] using short-term HVHF (35 l in 4 h, approx. 66–83 ml kg^{-1} h^{-1}) in severe refractory septic shock, reported dramatic improvement in MAP and perfusion in 11 of 20 patients, who were called responders. Retrospective analysis of data demonstrated that responders received a larger filtration dose.

Recently Joannes-Boyau described 24 septic-shock patients treated with long-term (96-h) HVHF at an ultrafiltration rate of 40–60 ml kg^{-1} h^{-1} [29]. Hemodynamic parameters improved significantly, similarly to results reported by Ratanarat et al. [30] in septic patients with renal failure.

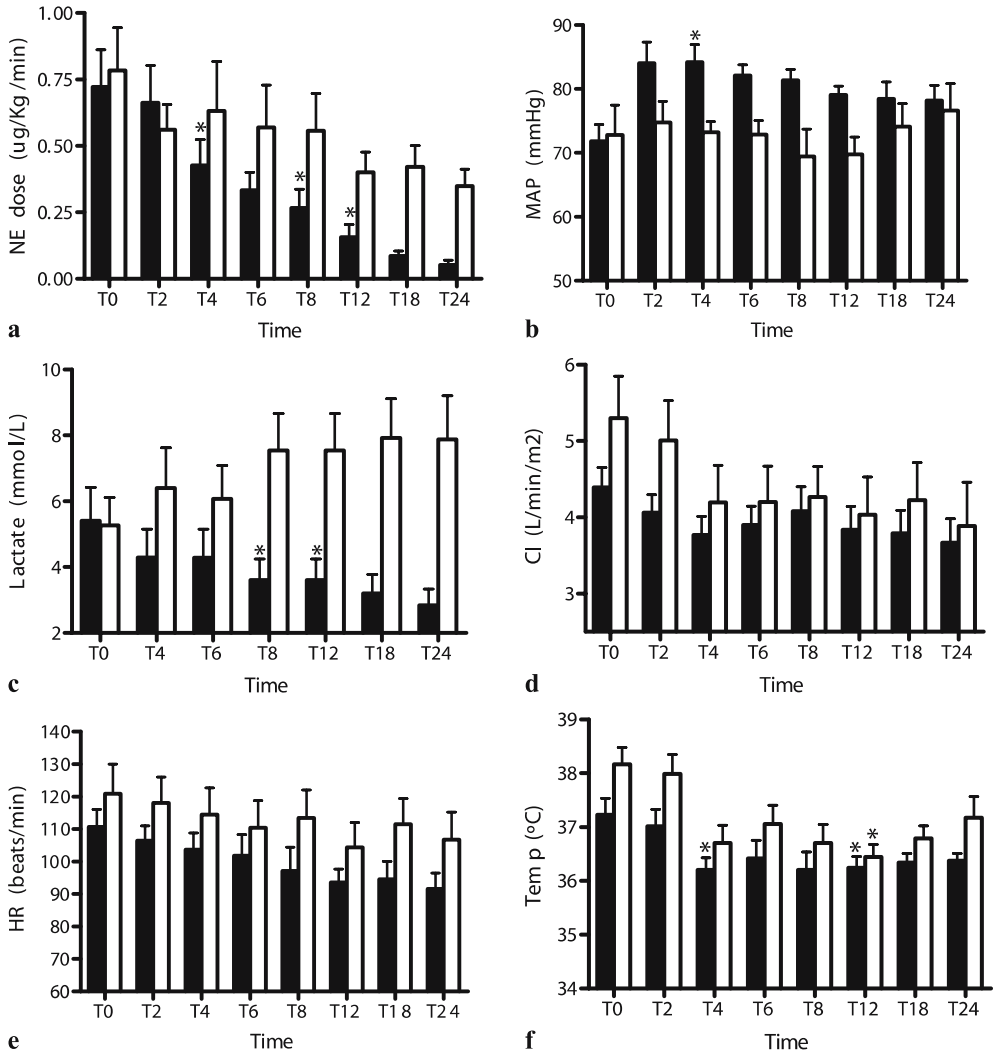

Fig. 2 Measurements after a 12-h single-session of high-volume hemofiltration in responders (*solid bars*) and nonresponders (*open bars*). **a** Course of norepinephrine (*NE*) dose. **b** Mean arterial pressure (*MAP*). **c** Arterial lactate (lactate). **d** Cardiac index (*CI*). **e** Heart rate (*HR*). **f** Temperature (*Temp*). $*p < 0.05$

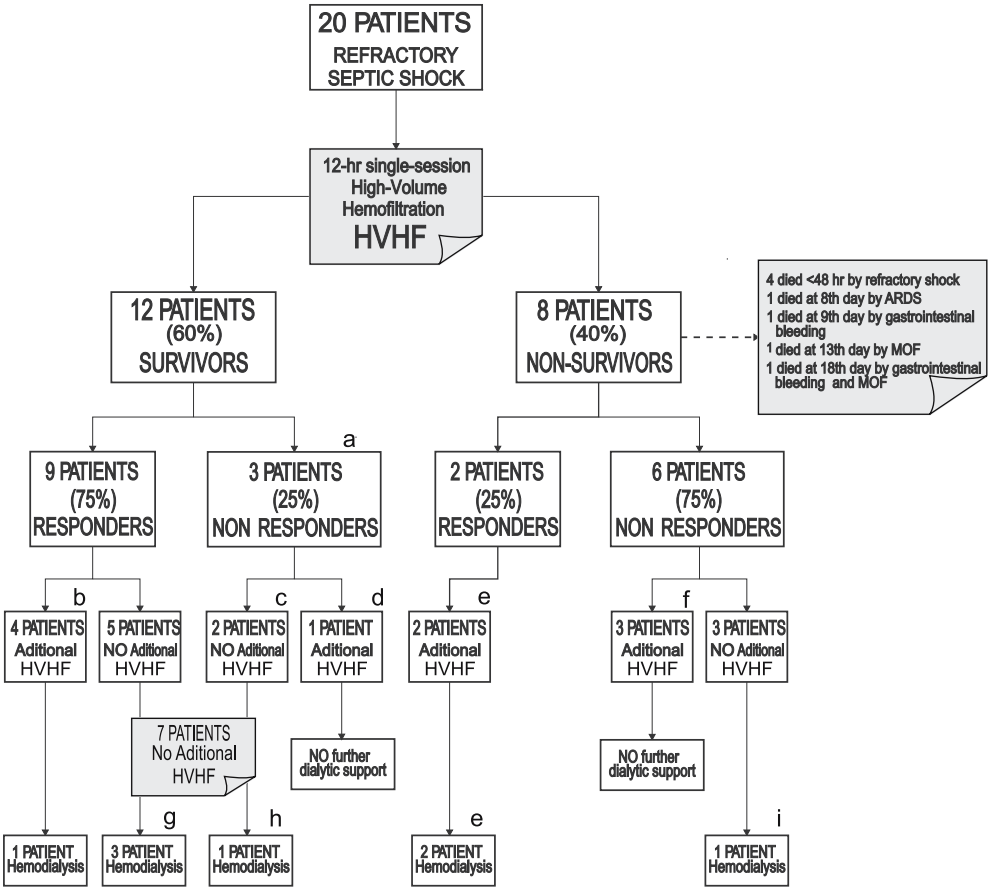

Fig. 3 Course and outcome of 20 patients who underwent HVHF, with regard to survival. *ARDS* Acute respiratory distress syndrome; *HD* hemodialysis; *MODS* multiorgan dysfunction syndrome. [a] The three patients showed delayed recovery from septic shock. [b] One patient received one more HVHF session, no HD sessions, two patients received two more HVHF sessions, no HD sessions, one patient received one more HVHF session, and seven further HD sessions. [c] Nonresponder only by lactate criteria; these patients did not receive further HVHF sessions. [d] Patient received two additional HVHF sessions. [e] One patient received one more HVHF session and four HD sessions; died on 9th day, one patient received three more HVHF session and ten further HD sessions; died on 18th day. [f] One patient received one more HVHF session; died at 36 h, one patient received one more HVHF session; died at 48 h, one patient received three more HVHF sessions, died on 13th day. [g] One patient received seven further HD sessions, one patient received eight further HD sessions, one patient with chronic renal failure. [h] Patient received four further HD sessions. [i] Patient received six further HD sessions

Finally, Cole et al. [31] found that conventional ultrafiltration rates (2 l/h) did not reduce organ dysfunctions after septic shock. Our findings, in concordance with the studies cited above, suggest a beneficial effect of high ultrafiltration rates. Other trials have focused mainly on renal function and included patients receiving different vasopressor schemes and/or diuretics and, in general, lower doses of NE or different depurative techniques [31, 32, 33]. According to the previous studies, we used a ultrafiltration rate of 100 ml kg^{-1} h^{-1}.

Comparison to other HVHF clinical studies

Hyperdynamic septic shock courses with cardiac index higher than 3 l min^{-1} m^{-2}. Our patients exhibited a mean CI of 4.71 l min^{-1} m^{-2}, this being a relevant difference from experimental reports (involving hypodynamic septic shock) and the studies of Honore et al. [22] and Joannes-Boyau et al. [29]. The Cole et al. [28] study was a crossover trial designed to test the effect of HVHF on NE requirements and clearance of inflammatory mediators. Their patients had an established need for renal replacement therapy and required lower doses of NE. We cannot compare our results with those of Ratanarat et al. [28] study because these authors did not set response criteria to HVHF and reported only the global course of hemodynamic parameters.

Another major difference is that we applied an algorithm incorporating most of the recent consensus recommendations to reduce mortality in sepsis shock [9] and included HVHF only at a final stage as salvage therapy. We consider standardization of hemodynamic protocols obligatory and beneficial [16, 34]. A comparison between previous trials and the present study is shown in S.T1 (see ESM).

Predictors of response

Unfortunately, no single variable at baseline proved useful in identifying patients who could benefit from HVHF in this setting. Responders and nonresponders were com-

parable at baseline in every variable, including delay of treatment in reference to onset of shock or to the moment at which severity threshold was reached. Nevertheless, at least 55% of these patients in severe refractory hyperdynamic septic shock responded to HVHF with a progressive resolution of shock, and this response was associated with better chance of survival since 81% of responders survived. Our only statistically significant predictor of survival was response to HVHF (odds ratio 9, 1.14–71.04; $p = 0.037$).

Because five nonresponders eventually exhibited a delayed resolution of shock, and three of them survived, we cannot rule out an effect of HVHF in at least slowing disease progression even more, if our selected criteria for starting HVHF or evaluating responsiveness are arbitrary. Interestingly, seven of the survivors required only one 12-h session of HVHF. Peak and current NE requirements are used in our algorithm to assess septic shock severity and requirements greater than $0.3\ \mu g\ kg^{-1}\ min^{-1}$ predict a more severe disease with mortality rates higher than 60% [15]. Thus, according to these data, HVHF appears to have potential as a salvage therapy when other standard treatments fail. What is the real place of HVHF in septic shock? The upcoming multicenter randomized study IVOIRE ("hIgh VOlume in Intensive care") will try to tackle this and other questions.

Place of high-volume hemofiltration in a septic shock management algorithm

Although the effect of HVHF on septic shock survival has not been evaluated in any randomized controlled trial, two small, noncontrolled trials suggest its usefulness as a salvage therapy in severe hypodynamic septic shock (expected mortality rates > 60%). Our patients, compared to those in the studies of Honore et al. [22] and Joannes-Boyau et al. [29], had a comparable very high mortality risk, yet at least 55% showed improved hemodynamics during HVHF, and responders exhibited a lower than expected mortality. These three studies taken together give some evidence-based support for the use of HVHF in severe hypo- or hyperdynamic septic shock patients. It appears rational to place HVHF at the final step of our algorithm, when other sequential recommended therapies (steroids and DrotAA) fail to improve hemodynamics or perfusion. HVHF may even work synergistically with previous protocolized therapies, according to the "bundle" theory [16, 34]. There is no clinical evidence that an earlier use would obtain better results, although we cannot rule out this possibility; future trials will address this point. The lack of a control group and the small population in the current study preclude more definitive conclusions.

Conclusions

We believe that our study contributes significantly to knowledge in the field of hemofiltration support in severe septic shock. First, it inserts HVHF in a hemodynamic management algorithm where the technique is considered only after other widely accepted treatments have been started, and after objective entry criteria have been attained. Second, it suggests a positive effect in a not well studied setting, such as hyperdynamic septic shock. Third, it establishes precise hemodynamic and metabolic goals as targets of therapy for one single-session HVHF. If these goals are accomplished at the end of the HVHF period, the probability of survival might be improved.

In summary, our results suggest that in patients with severe hyperdynamic septic shock treated with a hemodynamic algorithm incorporating current recommended therapies, HVHF as a final step (salvage therapy) improves hemodynamic and perfusion parameters and eventually survival.

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