Intensive Care Med (1992) 18:235–240

Intensive Care Medicine

High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig

A. F. Grootendorst[1], E. F. H. van Bommel[1], B. van der Hoven[1], L. A. M. G. van Leengoed[2] and A. L. M. van Osta[3]

[1] Department of Intensive Care, St. Clara Hospital, Olympiaweg 350, NL-3078 HT Rotterdam, The Netherlands
[2] Centraal Diergeneeskundig Instituut, Edelhertweg 14, NL-8119 PH Lelystad, The Netherlands
[3] Agricultural Mathematics Group, GLW-DLO, P.O. Box 100, NL-6700 Wageningen, The Netherlands

Received: 30 August 1991; accepted: 3 March 1992

Abstract. This study assessed the influence of continuous high volume hemofiltration on right ventricular function of pigs with endotoxin induced shock. Eighteen anesthetized and ventilated pigs were studied for 240 min after the start of infusion of 0.5 mg/kg endotoxin over 30 min. Right ventricular ejection fraction (RVEF) was measured by rapid response thermodilution technique. After endotoxin infusion, the pigs were randomly divided into 3 groups: group 1 as a control group, receiving endotoxin only, group 2 to observe the effects of zero balance high volume veno-venous hemofiltration with removal of ultrafiltrate at a rate of 6000 ml/h, and group 3 to evaluate the effect of the extracorporeal circuit itself on RVEF. The decline of RVEF in group 2 was less than in group 1 (0.04 ± 0.02 vs 0.21 ± 0.03 (mean ± SEM); $p < 0.001$). The decline of RVEF in group 3 (0.24 ± 0.02) was more pronounced than that in group 1 ($p < 0.05$). The differences in the course of RVEF between group 1 and group 2 could not be explained by differences in heart rate, preload or afterload. Cardiac output and mean arterial pressure were significantly higher in group 2 than in group 1 ($p < 0.01$). It is concluded that in this model, high volume hemofiltration improves RVEF and cardiac performance by removal of vasoactive mediators, responsible for myocardial depression.

Key words: Endotoxic shock – High volume hemofiltration – Cardiac function in sepsis – right ventricular ejection fraction

The hemodynamic abnormality of early septic shock consists of high cardiac output, hypotension and peripheral vasodilation [1]. Cardiac dysfunction is an early feature of sepsis and septic shock [2]. Left ventricular dysfunction is well documented in human septic shock [2, 3], and experimental shock [4, 5]. Recently, right ventricular dysfunction during septic shock has been shown to occur as well [6–10]. Some authors emphasize that cardiac depression in sepsis is a biventricular phenomenon, while others suggest that right ventricular dysfunction may occur in the absence of left ventricular dysfunction [6, 11].

Although cardiac depression during septic shock is well documented, much less is known about its reversal by therapeutic interventions. Besides volume loading and inotropic therapy, hemofiltration has been reported to improve cardiac performance in the setting of human [12], and experimental [4, 13, 14] septic shock. Whether hemofiltration does so by binding of mediators to the filter membrane or by removal of mediators via the ultrafiltrate has not been investigated.

We studied the effect of high volume hemofiltration on the course of right ventricular ejection fraction, measured by the rapid response thermodilution technique, in endotoxin induced shock in pigs. To clarify the role of binding of mediators to the filter, we included a group connected to the extracorporeal circuit, while clamping the ultrafiltrate line.

Material and methods

The protocol was approved by the ethics committee for animal experiments. Eighteen pathogen free pigs from our own herd were used. The average age was 18 weeks and the weight varied from 36–39 kg. They were premedicated with 300 mg ketamine i.m. After 15 min they received a mixture of 3% halothane, 50% oxygen, and 50% N_2O by facemask during 3 min. Thereafter they were orally intubated and ventilated (FiO_2 0.40, 12 breath/min), using a blender (SJO 1, Ohio medical products, Minneapolis, USA) and a volume-controlled ventilator (Oxylog, Draeger, Luebeck, Germany). After the minute volume was adjusted to an arterial PCO_2 of 38–42 mmHg, it was not changed during the experiment. Anesthesia was maintained with 6 mg/kg/h phenobarbital and 0.1 mg/kg/h pancuronium. A 30 cm 5F cannula (cavafix, 417375/9, Braun, Melsungen, Germany) was advanced into the femoral artery after cutdown and connected to a pressure transducer (P/N 966025/07, Baxter, Irvine, USA), positioned to the level of the left atrium. Blood pressure was measured by connecting the transducer to a monitor (Hewlett Packard, 78342A). A 7F rapid response thermodilution catheter (93A-431H-7, Baxter Healthcare Corp., Irvine, USA) was introduced into the superior caval vein via a percutaneous puncture, using an introducer sheath (CC-350B-8, Baxter Healthcare Corp., Irvine,

USA). The catheter was introduced under pressure monitoring into the pulmonary artery, the proximal port was positioned 3 cm above the tricuspid valve. This position was checked by pressure tracing before each set of cardiac output measurements. The catheter was connected to an ejection fraction/cardiac output monitor (REF-1, Baxter Healthcare Corp., Irvine, USA) and to a pressure transducer (P/N 966025-07, Baxter Healthcare Corp., Irvine, USA) connected to a Hewlett-Packard monitor (78342A). The transducer was positioned to the level of the left atrium. Right atrial pressure (RAP) was measured intermittently by connecting the transducer to the right atrial port (20 cm from the tip) of the TD catheter. The pulmonary and arterial pressures were monitored continuously; mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP) and pulmonary arterial wedge pressure (PAw) were measured intermittently and their values calculated electronically from the pressure curve. Right ventricular ejection fraction (RVEF) and cardiac output were measured by thermodilution technique. The injectate was cooled using an injectate coil (93-500, Baxter Healthcare Corp., Irwine, USA). The injectate temperature was measured online. Each measurement was started at the end of a ventilatory cycle. The average of 3 measurements was accepted as the value of each period. A double lumen catheter (DL6K, Impra. Inc., Tempe, AZ) was introduced into the subclavian vein via direct puncture. Each lumen was filled with 500 units of heparin in 1 ml Ringers lactate to prevent clotting. All pigs received 400 ml/h Ringers lactate throughout the experiment. The hemofiltration set up consisted of a roller pump, air detector and pressure limiter (Gambro AK 10, Lund, Sweden). A 0.6 m^2 polysulphone hollow fiber filter with a cut-off point of 30000 Dalton (Diafilter 30, Amicon Corp., Lexington, USA) was used. Prior to the experiment the filter was rinsed with 2 l Ringers lactate containing 5000 U heparin. Zero balance hemofiltration was achieved using a balance (BS 1 Gambro, Sweden). The substitution fluid (HF 21 hemofiltration solution, Fresenius, Bad Homburg, Germany) was warmed and infused before the filter. All pressures were recorded on a multi channel recorder (WS-682G, Nihon Kohden Co., Tokio, Japan). A Contraves 8016 Analyzer (Contraves AG, Zurich) was used to determinate leucocyte count and hemoglobin concentration.

After sampling of arterial blood with syringes (Sarstedt, Germany), blood gases were measured with an IL-1306 analyzer (Instrumentation Laboratories, USA).

Calculations were made as follows:

Systemic vascular resistance:

$$SVR = (MAP - RAP) \times 80/CO \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$$

Right ventricular stroke work:

$$RVSW = (MPAP - RAP) \times SV \times 0.0136 \text{ gm}$$

Left ventricular stroke work:

$$LVSW = (MAP - PAw) \times SV \times 0.0136 \text{ gm}$$

Stroke volume:

$$SV = CO/HR \text{ ml.}$$

Right ventricular enddiastolic volume:

$$RVEDV = SV/RVEF \text{ ml}$$

Experimental protocol

After instrumentation the pigs were allowed to stabilize for 60 min. From that moment on, hemodynamic measurements (RVEF, cardiac output, RAP, MPAP, PAw, MAP, heart rate) were performed every 30 min for 4 h. At the same time an arterial blood sample was drawn for blood gas measurement. After baseline measurements were made, endotoxin (0.111: B4, Sigma, St. Louis, USA) 0.5 mg/kg was infused over 30 min. After 30 min the pigs were randomized to serve as controls (group 1), to receive hemofiltration with ultrafiltrate removal (group 2) or to receive hemofiltration without ultrafiltrate removal, by clamping the ultrafiltrate line (group 3). In groups 2 and 3 the pump flow was set at 300 ml/min, in group 2 the ultrafiltrate flow was limited to 6000 ml/h. From 30 min on, all pigs received heparin 1500 U/h. In groups 2 and 3 the pump was stopped during cardiac output measurement. After 240 min the pigs were sacrificed.

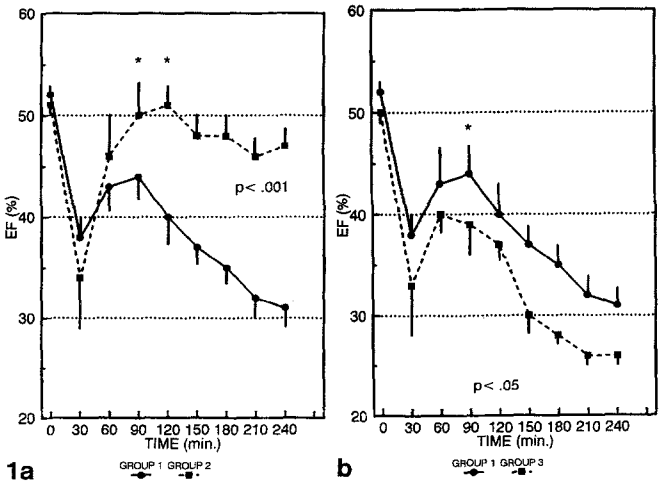
Statistical analysis

To compare the profiles of group 1 with the two treatment groups at different time points, statistical analysis was performed on all variables, using the ante-dependence method for repeated measurements, as described by Kenward [15–17]. This method can decompose observations into independent components. In particular, it is possible to identify the first moment at which a new significant difference between profiles occurs. In addition, this method provides a cumulative overall test to compare profiles.

To estimate the effects of treatments, analysis of variance was performed on variables measured at the start and at the end of the experiment, after 240 min, using the pigs as a block. This was done to show how much variables actually changed during the experiment. Moreover, estimated contrasts using Fisher's LSD is given, being the least difference between two effects that is significant and a measure of precision of the estimated difference [15, 16]. To analyze changes of variables within the groups, Students *t*-test was used.

Results

Seventeen of the 18 pigs survived till the end of the experiment, one pig in group 3 died at 130 min. The hemodynamic data are shown in Table 1 and depicted in Figs. 1–4. Table 1 also shows the results of the overall tests of comparison between the profiles of the variables of group 2 versus group 1 and group 3 versus group 1. The asteriskes in the figures show the time points at which a new difference between the groups occurred, $p < 0.05$ considered significant. Table 2 shows the estimat-



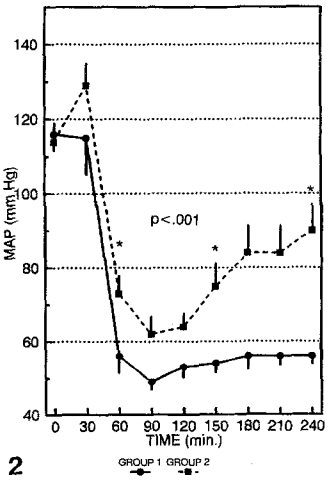


Fig. 1a, b. RVEF in group 1 ($n = 6$) and group 2 ($n = 6$) **(a)**, and group 1 and group 3 ($n = 6$; one pig died after 130 min) **(b)**, after endotoxin infusion. The means ± SEM are shown. The P-value results from the overall tests of comparison of RVEF profiles. * : $p < 0.05$, using the antedependence method

Fig. 2. MAP after endotoxin infusion in group 1 ($n = 6$) and 2 ($n = 6$). The means ± SEM are shown. The *p*-value results from the overall tests of comparison of MAP profiles. * : $p < 0.05$, using the antedependence method

Table 1. Variables of groups 1, 2 and 3 at different time points (mean ± SEM). The course of each variable in group 2 and 3 was compared to its course in group 1, using the antedependence method

		Time (min)												Antedependence method
		0	30	60	90	120	150	180	210	240	
MAP	1	116 ±2.1	115 ±8.4	56 ±3.3	49 ±1.5	53 ±2.0	54 ±1.4	56 ±3.3	56 ±3.1	56 ±2.2	
(mmHg)	2	114 ±2.7	129 ±7.7	73 ±4.4	62 ±4.0	75 ±5.6	75 ±5.6	84 ±7.2	84 ±6.9	90 ±7.5	$p<0.001$
	3	118 ±1.4	122 ±4.1	64 ±4.0	53 ±3.4	52 ±4.1	52 ±4.1	51 ±4.1	47 ±4.3	49 ±2.3	NS
MPAP	1	14 ±1.7	32 ±3.1	20 ±2.9	24 ±3.4	29 ±3.0	29 ±1.8	30 ±1.3	29 ±1.4	29 ±2.0	
(mmHg)	2	14 ±1.3	37 ±2.1	21 ±2.1	27 ±1.9	27 ±3.3	30 ±2.5	32 ±2.4	34 ±2.5	34 ±1.5	NS
	3	15 ±2.7	39 ±3.0	24 ±3.0	30 ±3.8	35 ±3.9	36 ±4.7	36 ±3.9	36 ±4.3	39 ±3.5	NS
PAwP	1	4 ±0.5	4 ±0.7	4 ±1.0	5 ±1.8	4 ±1.4	4 ±1.0	6 ±1.5	5 ±1.2	6 ±1.7	
(mmHg)	2	5 ±1.2	5 ±0.6	3 ±1.1	3 ±0.7	4 ±1.0	5 ±1.1	4 ±0.9	5 ±0.7	5 ±0.7	NS
	3	4 ±0.6	7 ±2.6	4 ±2.4	7 ±3.0	5 ±1.7	6 ±2.4	6 ±2.3	7 ±2.2	8 ±2.6	NS
HR	1	118 ±8.0	124 ±7.3	141 ±7.9	138 ±7.6	138 ±7.6	139 ±4.9	140 ±5.3	138 ±6.2	138 ±7.4	
(bpm)	2	129 ±3.4	124 ±6.9	134 ±7.4	129 ±3.4	126 ±3.4	123 ±4.3	119 ±4.7	113 ±3.9	115 ±2.8	NS
	3	142 ±5.1	130 ±10.4	141 ±5.5	142 ±8.4	133 ±8.8	136 ±10.4	133 ±9.7	132 ±11.1	131 ±10.6	NS
RAP	1	1 ±0.3	1 ±0.2	1 ±0.4	2 ±0.3	2 ±0.3	2 ±0.6	2 ±0.6	2 ±0.6	2 ±0.6	
(mmHg)	2	1 ±0.0	1 ±0.5	1 ±0.3	1 ±0.2	2 ±0.6	2 ±0.5	2 ±0.6	2 ±0.4	2 ±0.4	NS
	3	2 ±0.7	2 ±0.6	2 ±0.8	2 ±0.3	3 ±0.7	2 ±1.0	3 ±1.0	2 ±0.8	3 ±1.0	NS
CO	1	6.3 ±0.26	4.7 ±0.38	5.6 ±0.36	5.8 ±0.45	5.5 ±0.45	5.5 ±0.38	4.8 ±0.41	4.5 ±0.48	4.8 ±0.77	
(l/min)	2	7.2 ±0.37	4.5 ±0.65	6.7 ±0.71	7.7 ±0.58	7.7 ±0.56	7.4 ±0.34	6.8 ±0.44	6.8 ±0.40	6.8 ±0.22	$p<0.01$
	3	7.3 ±0.45	4.9 ±1.16	5.7 ±0.39	5.5 ±0.45	5.0 ±0.39	4.4 ±0.16	3.9 ±0.28	3.3 ±0.27	3.4 ±0.08	$p<0.02$
SVR	1	1478 ±64.3	2048 ±264.9	801 ±87.7	663 ±52.5	771 ±56.5	817 ±60.0	921 ±64.5	988 ±83.5	1005 ±116.5	
(dynes·s·cm^{-5})	2	1283 ±72.9	2492 ±300.9	926 ±133.4	656 ±80.6	662 ±64.3	807 ±79.2	988 ±125.8	993 ±145.9	1004 ±112.3	NS
	3	1295 ±74.9	2364 ±332.5	873 ±63.7	774 ±61.2	844 ±62.8	895 ±70.1	1030 ±137.5	1146 ±146.4	1076 ±70.1	NS
RVSM	1	9 ±0.9	16 ±1.1	10 ±1.5	12 ±1.3	15 ±1.9	13 ±0.8	13 ±0.5	12 ±0.7	12 ±0.7	
(gm)	2	10 ±1.6	19 ±4.6	13 ±2.2	20 ±1.9	21 ±2.4	22 ±2.1	24 ±2.8	26 ±2.6	26 ±1.1	$p<0.001$
	3	9 ±1.9	19 ±4.5	12 ±1.3	14 ±2.1	16 ±2.9	15 ±1.0	13 ±1.4	11 ±1.4	13 ±1.1	NS
LVSW	1	84 ±7.9	57 ±4.8	28 ±2.8	26 ±3.3	27 ±2.9	25 ±2.2	24 ±2.6	23 ±2.2	23 ±2.7	
(gm)	2	83 ±4.3	64 ±12.7	48 ±5.1	48 ±4.3	49 ±2.9	56 ±4.3	61 ±7.6	64 ±5.2	69 ±7.6	$p<0.001$
	3	79 ±2.8	61 ±14.7	34 ±5.8	27 ±6.5	26 ±4.6	22 ±3.8	18 ±2.5	15 ±3.0	15 ±20	$p<0.05$
EF	1	0.52±0.01	0.38±0.02	0.43±0.04	0.44±0.03	0.40±0.03	0.37±0.02	0.35±0.02	0.32±0.02	0.31±0.02	
	2	0.51±0.01	0.34±0.06	0.46±0.04	0.50±0.03	0.51±0.02	0.48±0.02	0.48±0.02	0.46±0.02	0.47±0.02	$p<0.001$
	3	0.50±0.01	0.33±0.05	0.40±0.02	0.39±0.03	0.37±0.02	0.30±0.02	0.28±0.01	0.26±0.01	0.26±0.01	$p<0.05$
EDV	1	100 ±5.4	103 ±7.0	98 ±8.0	100 ±4.6	102 ±5.4	102 ±7.0	100 ±7.44	102 ±5.0	108 ±8.7	
(ml)	2	108 ±6.7	111 ±5.7	111 ±6.4	120 ±6.9	119 ±4.5	125 ±4.5	120 ±6.66	128 ±5.6	125 ±3.3	NS
	3	102 ±2.9	105 ±10.6	102 ±6.6	100 ±10.5	106 ±15.8	101 ±13.91	96 ±14.5	92 ±13.4	96 ±14.9	NS
SV	1	52 ±3.9	42 ±4.4	41 ±3.6	43 ±4.0	40 ±3.2	38 ±3.2	35 ±2.5	33 ±2.8	34 ±4.3	
(ml)	2	56 ±3.5	38 ±7.9	51 ±6.1	59 ±6.2	61 ±5.0	60 ±3.9	57 ±4.2	59 ±3.5	60 ±2.9	$p<0.001$
	3	50 ±1.4	39 ±7.5	42 ±3.8	45 ±6.4	42 ±4.7	35 ±4.1	28 ±3.0	28 ±2.9	27 ±2.2	$p<0.05$
pO_2	1	182 ±1.2	144 ±17.4	117 ±17.4	115 ±13.4	116 ±12.2	119 ±12.2	110 ±10.8	99 ±6.9	96 ±11.2	
(mmHg)	2	167 ±8.5	154 ±19.5	163 ±11.6	154 ±13.4	144 ±13.8	142 ±18.2	148 ±19.1	149 ±23.0	142 ±21.8	$p<0.05$
	3	182 ±1.0	111 ±25.5	94 ±14.4	89 ±15.8	91 ±17.4	99 ±22.6	94 ±22.5	100 ±29.1	97 ±28.8	NS

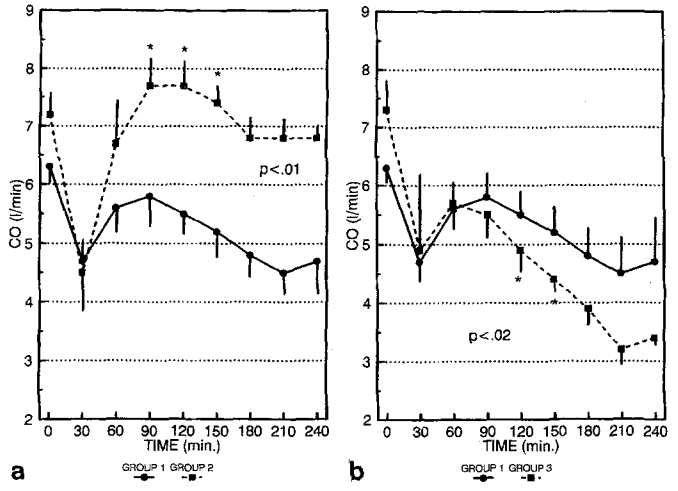


Fig. 3a, b. Cardiac output in group 1 ($n = 6$) and group 2 ($n = 6$) (**a**), and group 1 and group 3 ($n = 6$; one pig died after 130 min) (**b**), after endotoxin infusion. The means ± SEM are shown. The p-value results from the overall tests of comparison of cardiac output profiles. *: $p < 0.05$, using the antedependence method

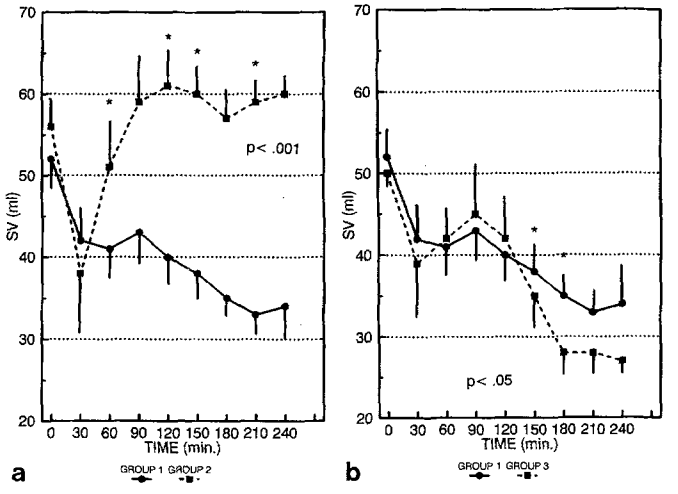


Fig. 4a, b. SV after endotoxin infusion in group 1 ($n = 6$) and group 2 ($n = 6$) (**a**) and group 1 and group 3 ($n = 6$; one pig died after 130 min) (**b**). The means ± SEM are shown. The p-value results from the overall tests of comparison of SV profiles. *: $p < 0.05$, using the antedependence method

ed increase or decrease at 240 min compared to baseline values, using Fisher's LSD.

Group 2 versus group 1

At the end of endotoxin infusion RVEF had decreased in both groups (Fig. 1a). In group 2 RVEF returned to its baseline value after 60 min of hemofiltration, whereas only a partial restoration of RVEF in group 1 was observed during this period. After 90 min, RVEF fell further in group 1 than in group 2, resulting in a markedly higher RVEF in group 2 at the end of the experiment. From 90 to 240 min RVEF in group 1 declined from 0.44 ± 0.03 to 0.31 ± 0.02 ($p < 0.05$), while no significant changes in RVEDV, MPAP or HR occurred in this period. MPAP and RVEDV, important determinants of RVEF, did not differ between the two groups. At 240 min, HR was lower in group 2 than in group 1, but no overall difference was seen between the two groups. MAP dropped in both groups after endotoxin infusion was completed. The drop, however, was less severe at 60 min in group 2 than in group 1. From 150 min on, partial restoration of MAP was observed in group 2, while it remained low in group 1 (Fig. 2). This difference in the course of MAP was caused by differences in cardiac output (Fig. 3a), as no differences in the course of SVR occurred. SV, the course of which is shown in Figure 4a, decreased in both groups at the end of endotoxin infusion. After this initial decrease, SV dropped further in Group 1, while it returned to baseline value in group 2 after 60 min of hemofiltration. After 60 min, SV in group 2 remained higher than baseline in group 1. No differences in the course of RAP between the two groups were seen. Arterial PO_2 in group 2 was higher than that in group 1.

Table 2. Fisher's LSD-test 240 versus 0 min; $p < 0.05$

	Group 2-1	Group 3-1	LSD 2-1	LSD 3-1
MAP	36.0*	−9.5	16.30	17.10
MPAP	5.6	11.5*	7.85	8.23
Wedge	−1.84	2.53	5.11	5.36
HR	−34.6*	−28.7*	23.27	24.41
RA	0.34	0.57	2.31	2.42
CO	1.19*	−1.91*	1.17	1.23
SVR	234	184	266.8	279.9
RVSW	13.34*	3.07	4.56	4.78
LVSW	47.7*	1.8	22.03	23.10
EF	0.190*	−0.035	0.0893	0.0880
EDV	8.6	−14.0	28.34	29.72
SV	22.5*	−4.1	10.68	11.20
PO_2	62.0*	5.0	57.27	60.07
WBC	−0.48	−0.19	1.845	1.935
Hb	0.107	0.32	1.572	1.649

* Indicates $p < 0.05$; LSD, least significant difference

Group 3 versus group 1

Figure 1b shows the course of RVEF after the start of endotoxin infusion. At 240 min, MPAP in group 3 was higher than that in group 1, but no overall differences were seen. No differences in the courses of RVEDV, HR, MAP and SVR were seen. As can be seen from Figs. 3b and 4b, cardiac output and SV, respectively, decreased further in group 3 than those in group 1. One pig in group 3 died of respiratory failure 130 min after the endotoxin infusion. Data of this pig was included in the statistical analysis.

Discussion

Left ventricular dysfunction is a well documented phenomenon in sepsis and septic shock [2, 9]. Parker et al. found decreased left ventricular ejection fraction (LVEF) in survivors of septic shock, associated with a dilated left ventricle [18]. Natanson et al. found substantial decreases in LVEF in dogs after implantation of an infected clot in-

to the peritoneum [19]; following adequate volume loading the dogs manifested left ventricular dilation. Although some of these studies show that endotoxin can reduce LVEF, it was recently demonstrated that depressed LVEF can occur in the absence of endotoxemia as well [20].

Right ventricular function in septic shock has not been studied as well as left ventricular function. Kimchi et al. reported right ventricular dysfunction, characterised by depressed RVEF, in patients with septic shock [6]. Importantly, several of these patients demonstrated a significant depression of RVEF while left ventricular function remained normal. Recently, Parker et al. demonstrated right ventricular dysfunction in septic shock patients, similar to left ventricular dysfunction [11].

Data on right ventricular dysfunction in animal models of septic shock is scarce. Schneider et al. found depressed right ventricular performance in *E. coli* shock in pigs [4].

In our study, endotoxin infusion induced a decrease in RVEF, while no change in EDV was seen. Although the initial decrease in RVEF is at least partially explained by the increase in MPAP, no change in MPAP was seen from 90–240 min while in the same period a significant decrease in RVEF occurred. This suggests deterioration of intrinsic right ventricular function.

Acidosis, subendocardial ischemia and decreased coronary blood flow have all been incremented as possible causes for the ventricular dysfunction in sepsis [21]. Several recent studies, however, have documented depressed left ventricular function in the absence of decreased coronary flow and myocardial ischemia, rendering their role in cardiac dysfunction in sepsis questionable [21, 22].

Recently, attention has been focused on circulating, filtrable myocardial depressant substances that might be responsible for the myocardial depression in sepsis [24, 25].

In another study, myocardial edema was found to occur in a rat model of multiple organ failure [26]. The authors felt that this myocardial edema might be the cause of the myocardial dysfunction in septic shock. Moreover, the authors emphasize the analogy between the microvascular changes, seen in the heart and in all other organs studied [26, 27]. These changes were suggested to be the effect of liberation of vasoactive mediators during sepsis, that potentionally could be removed by hemofiltration [12, 26, 27].

In contrast to many data available on cardiac dysfunction in sepsis, very few data are available on the efficacy of therapeutic interventions aiming at its reversal. Low volume hemofiltration (0.6 l/h ultrafiltrate) has been shown to improve left ventricular contraction velocity in a dog model of septic shock, but failed to improve stroke volume or systemic blood pressure [4]. In another study low volume hemofiltration (0.6 l/h ultrafiltrate) marginally improved cardiac output in a porcine endotoxic shock model [14].

The more pronounced effect of hemofiltration on cardiac function and blood pressure in our study compared to the others is probably explained by the much higher ultrafiltrate volumes we achieved.

More importantly, our study is the first study to assess the effect of high volume hemofiltration on RVEF. Our results show that the drop in RVEF after endotoxin infusion can almost completely be reversed by high volume hemofiltration. The extracorporeal circuit not only failed to reverse the drop in RVEF but even induced an additional decrease in RVEF. Therefore, the possibility of a beneficial effect of the extracorporeal circuit, caused by binding of vasoactive mediators to the filter, can be excluded.

From 30–90 min RVEF increased further in the hemofiltered group than in the control group. In the same period, no differences occurred in MPAP, heart rate, MAP or RVEDV. Deductively, the increase in RVEF is probably explained by an increase of right ventricular contractility. Whether this is caused by the removal of filtrable myocardial depressant substances, as has been shown to occur during hemofiltration [28], or by the removal of vasoactive mediators that are responsible for myocardial edema [26], cannot be concluded from our data. In the latter case, however, a concomitant increase of SVR and cardiac function would be expected to occur in our study. In contrast, our results indicate that hemofiltration improves cardiac function but does not reverse peripheral vasodilation after endotoxin infusion, suggesting different etiologies of the cardiac dysfunction and the drop in SVR by endotoxin.

LVSW in group 2 was higher than that in group 1. As no differences in PAwP occurred between these two groups, this indicates that hemofiltration improves left as well as right ventricular function, possibly by the removal of substances, responsible for the biventricular failure described in other studies [11].

As long as no data are available on the efficacy of inotropic drugs in the reversal of sepsis induced right ventricular dysfunction, no conclusion can be made concerning the potential clinical relevance of our findings. Hemofiltration, however, might well be a more useful therapy than inotropic therapy, as it removes the cause of the cardiac dysfunction. Septic shock involves much more than hypotension and depressed cardiac function. Hemofiltration has the potential to remove many of the mediators, known to play a role in sepsis and septic shock. This study shows that high volume hemofiltration can partially reverse one of the most striking, albeit not necessarily the most important, features of septic shock i.e. cardiac dysfunction.

Therefore, further research is justified to assess the potential of high volume hemofiltration as part of the treatment of septic shock.

Acknowledgement. This study was supported by a grant from the Kunstmatig Niercentrum Rotterdam Foundation.

References

1. Rackow EC, Astiz ME (1991) Pathophysiology and treatment of septic shock. JAMA 226:548–554
2. Parker MM (1990) Cardiac dysfunction in human septic shock, pp 229–230. In: Parrillo JE (moderator) Septic shock in humans: ad-

vances in the understanding of pathogenesis, cardiovascular dysfunction and therapy. Ann Intern Med 113:227–242
3. Cunnion RE, Parrillo JE (1989) Myocardial dysfunction in sepsis. Recent insights. Chest 95:941–945
4. 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
5. Guntheroth WG, Jonathan PJ, Kawabori I, Stevenson JG, Moreno AH (1982) Left ventricular performance in endotoxin shock in dogs. Am J Physiol 242:172–176
6. Kimchi A, Ellrodt AG, Berman DS, Riedinger MS, Swan HJC, Murata GH (1984) Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. J Am College Cardiol 4:945–951
7. Hoffman MJ, Greenfield LJ, Sugerman HJ, Tatum JL (1983) Unsuspected right ventricular dysfunction in shock and sepsis. Ann Surg 198:307–319
8. Schneider AJ, Teule GJJ, Groeneveld ABJ, Nauta J, Heidendal GAK, Thijs LG (1988) Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. Am Heart J 116:103–112
9. Abel FL (1990) Does the heart fail in endotoxin shock? Circ Shock 30:5–13
10. Vincent JL, Reuse C, Frank N, Contempre B, Kahn RJ (1989) Right ventricular dysfunction in septic shock: assessment by measurements of right ventricular ejection fraction using the thermodilution technique. Acta Anaesthesiol Scand 33:34–38
11. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE (1989) Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression in humans. Chest 97:126–131
12. Gotloib J, Barzilay E, Shustak A, Wais Z, Jaichenko J, Lev A (1986) Hemofiltration in septic ARDS. The artificial kidney as an artificial endocrine lung. Resuscitation 13:123–132
13. Staubach KH, Rau HG, Kooistra A, Schardey HM, Hohlbach G, Schildberg FW (1989) Can hemofiltration increase survival time in acute endotoxemia – a porcine shock model. Prog Clin Biol Res 308:821–826
14. Stein B, Pfenninger E, Grunert A, Schmitz JE, Hudde M (1990) Influence of continuous hemofiltration on hemodynamics and central blood volume in experimental endotoxic shock. Intensive Care Med 16:494–499
15. Kenward MG (1987) A method for comparing profiles of repeated measurements. Appl Stat 36:296–308
16. Payn RW (1987) Genstat5, reference manual. Clarendon Press, Oxford
17. Genstat5 (1989) Procedure library manual. Numerical Algorithm Group, Oxford, 1989
18. Parker MM, Suffredini AF, Natanson C, Ognibene FP, Shelhamer JH, Parrillo JE (1989) Responses of left ventricular function in survivors and nonsurvivors of septic shock. J Crit Care 4:19–25
19. Natanson C (1990) A canine model of septic shock, pp 231–232. In: Parrillo JE, moderator. Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction and therapy. Ann Intern Med 113:227–242
20. Natanson C, Danner RL, Elin RJ, Hosseini JM, Peart KW, Banks SM, MacVittie TJ, Walker RI, Parrillo JE (1989) Role of endotoxemia in cardiovascular dysfunction and mortality. E. coli and St. aureus challenges in a canine model of human septic shock. J Clin Invest 83:243–251
21. Adams HR, Parker JL, Laughlin MH (1990) Intrinsic myocardial dysfunction during endotoxemia: dependent or independent of myocardial ischemia? Circ Shock 30:63–76
22. Cunnion RE, Shaer GL, Parker MM, Natanson C, Parrillo JE (1986) The coronary circulation in human septic shock. Circulation 73:637–644
23. Dhainaut JH, Huyghenbaert MF, Monsallier JH, Lefevre G, Dall'Ava-Santucci J, Brunet F (1987) Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose and ketones in patients with septic shock. Circulation 75:533–541
24. Parrillo JE, Beuch C, Shelhamer JH, Parker MM, Natanson C, Schuelte W (1985) A circulating myocardial depressant substance in humans with septic shock. J Clin Invest 76:1539–1553
25. Reilly JM, Cunnion RE, Burch-Whitman C, Parker MM, Shelhamer JH, Parrillo JE (1989) A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. Chest 95:1072–1080
26. Gotloib L, Shustak A, Galdi P, Jaichenko J, Fudin R (1991) Loss of microvascular negative charges accompanied by interstitial edema in septic rats' heart. Circ Shock (in press)
27. Gotloib L, Shustak A, Jaichenko J, Galdi P (1988) Decreased density distribution of mesenteric and diafragmatic microvascular anion charges during murine abdominal sepsis. Resuscitation 16:179–192
28. Coraim FJ, Coraim HP, Eberman R, Stellwag FM (1986) Acute respiratory failure after cardiac surgery: clinical experience with the application of continuous arteriovenous hemofiltration. Crit Care Med 14:714–718

A. F. Grootendorst, MD
Department of Intensive Care
St. Clara Hospital
Olympiaweg 350
NL-3078 HT Rotterdam
The Netherlands