Anesthesiology 2006; 104:1216–22

Blood Warming during Hemofiltration Can Improve Hemodynamics and Outcome in Ovine Septic Shock

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Background: **This study was designed to evaluate the effects of blood warming during hemofiltration on global and regional hemodynamics, plasma lactate, and 24-h survival during septic shock.**

Methods: **Twenty anesthetized and mechanically ventilated sheep underwent induction of peritonitis and, 4 h later, were treated by hemofiltration with (n = 10) or without (n = 10) blood warming.**

Results: **In the group without blood warming, body temperature decreased after starting hemofiltration and remained below baseline. In the other animals, body temperature stabilized at baseline level during hemofiltration and increased to a maximum of 40.8°C thereafter. The group without warming experienced a decrease in blood pressure (from 90 mmHg to 38 mmHg) and cardiac output (from 4.0 l/min to 2.3 l/min). Metabolic acidosis and the increase in lactate were less marked when temperature was maintained. None of the animals without warming but all of the animals with warming survived to 16 h.**

Conclusions: **Differences in temperature during hemofiltration resulted in striking differences in hemodynamics, metabolic acidosis, and survival rate in this clinically relevant experimental model of septic shock.**

DURING the past decade, hemofiltration has often been used as a supportive therapy for acute renal failure.[1–3] Many patients treated with this technique have underlying sepsis. Hemofiltration has also been used to counteract the inflammatory response induced by cardiopulmonary bypass.[4] Like any form of extracorporeal circuit, hemofiltration often results in a small decrease in body temperature. Fifty percent of critically ill patients undergoing continuous veno-venous hemofiltration (CVVH) with high ultrafiltration rates have a body temperature less than 35.5°C for more than 24 h after the start of CVVH.[5,6] The clinical consequences of this decrease in temperature remain unclear.

Hypothermia is correlated with increased mortality not only in animal sepsis models,[7–10] but also in patients with septic shock.[11–14] During the past few years, our laboratory has developed an ovine model of sepsis induced by fecal peritonitis, which resembles human septic shock.[15,16] The aim of the current study was to investigate whether, by using a blood warmer, prevention of the decrease in body temperature induced by CVVH could influence outcome in this model.

Materials and Methods

The study was approved by the Ethical Committee of Animal Research at the Erasme University Hospital, Brussels, Belgium, and care and handling of the animals were in agreement with National Institutes of Health guidelines.

Surgical Preparation

Twenty female sheep weighing 31.5 ± 4.5 kg were anesthetized with 0.1 mg · kg^{-1} · h^{-1} midazolam and 0.1 μg · kg^{-1} · min^{-1} fentanyl (Infusion pump Infusomat 11; Braun, Melsungen, Germany). The trachea was intubated with a No. 8 cuffed endotracheal tube, and each animal was ventilated (Servo ventilator 90OC; Siemens-Elema, Solna, Sweden). Inspired oxygen fraction was adapted to keep arterial oxygen partial pressure (Pa_{O_2}) between 70 and 100 mmHg. Controlled ventilation was facilitated with pancuronium bromide (0.15 mg/kg initially, with supplementation at 0.075 mg · kg^{-1} · h^{-1} thereafter). Respiratory frequency was set at 16 breaths/min, and tidal volume was set at approximately 8 ml/kg to obtain an initial end-tidal carbon dioxide tension (4721 OA Capnometer; Hewlett-Packard, Waltham, MA) between 35 and 45 mmHg. A positive end-expiratory pressure of 7.5 cm H_2O was installed after the surgical procedure for the rest of the experiment. The right forepaw vein was catheterized for intravenous administration of midazolam and fentanyl. The right femoral artery was catheterized for monitoring of arterial blood pressure and withdrawal of arterial blood samples. The left femoral artery was catheterized with a single lumen catheter (JO-KATH, CP-1 175; Hechingen, Germany) for access to the hemofiltration machine. Through the right external jugular vein, a balloon-tipped pulmonary artery catheter (744HF75 7.5F; Edwards Lifesciences, Unterschleissheim, Germany) was placed under guidance of pressure waves (monitor Sirecust 302A; Siemens, Erlangen, Germany). A single-lumen catheter (JO-KATH, CP-1 175) was placed in the same right jugular vein for connection to the hemofiltration machine. A midline laparotomy was performed, and an ultrasonic flow probe was placed around the mesenteric artery (4 mm), for measurement of blood flow. The probe was connected to a blood

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Received from the animal laboratory of Erasme University Hospital, Brussels, Belgium. Submitted for publication June 16, 2005. Accepted for publication January 27, 2006. Support was provided solely from institutional and/or departmental sources.

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flowmeter (model T208; Transonic Systems, Ithaca, NY), which was calibrated before each experiment. A gastric tonometer catheter was placed in an ileal loop. A cecotomy of 1 cm was performed, and approximately 2 cm of fecal content was pushed into the abdomen. The cecum and then the abdomen were closed. The urinary bladder was catheterized per urethra with a No. 18 Foley catheter. Thereafter, the animal was turned prone for the rest of the experiment. After a 30-min stabilization period, the first measurements were performed.

Study Design

All animals received 2 l lactated Ringer's solution during the surgical procedure and 10–15 ml · kg^{-1} · h^{-1} during the rest of the experiment, with a rate adjusted to keep pulmonary artery occlusion pressure around the baseline level. Hemofiltration was started 4 h after the onset of peritonitis at 100 ml · kg^{-1} · h^{-1} for 10 h. We used a polysulphone (PSHF 700 G; Baxter Healthcare, Irvine, CA) or a high-cutoff polyamide membrane (P2SH; Gambro, Hechingen, Germany), which have been shown to increase survival in other sepsis models.[17,18] The experiment was continued until death of the animal, or for 24 h. The first five experiments resulted in disappointing results, with all animals dying within 12 h. The addition of a blood warmer in the following five experiments resulted in a dramatic increase in survival time. We completed these observations in an additional group of 10 experiments in which sheep were randomized, using envelops, to hemofiltration with or without blood warming. The combined results are presented.

Hemofiltration Setting

The hemofiltration device consisted of a roller pump, air detector, and pressure feedback system (BM 11/BM 14; Edwards Lifesciences). A 1-m^2 polysulphone (PSHF 700 G) and a 1.1-m^2 polyamide hollow fiber filter (P2 SH) were used. Before the experiment, the filter was rinsed with 1 l normal saline containing 5,000 U heparin. Zero balance hemofiltration was achieved using a balance installed in the device. This was fully automated, resulting in constant ultrafiltration rates. The buffer solution, containing 30 mEq/l bicarbonate, 2.9 mEq/l lactate, and other electrolyte ions (Hemosol; Hospal, Lyon, France), was warmed to 39°C and infused after the filter. A heparin infusion of 1,000 U/h was given during hemofiltration. In the group with a blood warmer, the blood warmer (Prismatherm; Hospal) was inserted on the venous line, immediately before return to the animal.

Measurements and Calculations

All parameters were recorded every hour. Heart rate and pressures from femoral arterial and pulmonary arterial lines were monitored continuously using pressure transducers (series 966020-01; Baxter Healthcare) with amplifiers (Heilige Servomed, Freiburg, Germany) and a pen recorder (model 2600 S; Gould Instruments, Cleveland, OH). All pressures were determined at end expiration. Cardiac output (l/min) was measured by the thermodilution technique, using three to five 5-ml bolus injections of cold 5% dextrose in ice water at end expiration. Continuous cardiac output was also recorded (Vigilance, Baxter Healthcare). Stroke volume, left ventricular stroke work, systemic vascular resistance (SVR), and pulmonary vascular resistance were calculated according to the standard formulas. Core temperature was recorded from the pulmonary artery catheter.

Exhaled gases were directed through a mixing chamber for sampling of expired oxygen fraction and end-tidal carbon dioxide. The gas analyzers for expired oxygen (P.K. Morgan, Chatham, Kent, United Kingdom) and carbon dioxide (47210A capnometer; Hewlett Packard, Waltham, MA) were calibrated before the experiment. Expired minute volume was measured with a spirometer (Haloscale Wright Respirometer; Edronton, United Kingdom) over a 2-min period. Arterial and mixed venous blood samples were simultaneously withdrawn for immediate determination of blood gases (ABL 2; Radiometer), hemoglobin, and oxygen saturation (OSM 3 hemoximeter calibrated for animal blood; Radiometer). Systemic oxygen consumption and systemic oxygen delivery were calculated according to standard formulas. Oxygen extraction ratio was derived from the ratio of oxygen consumption/oxygen delivery.

Blood lactate concentrations were measured using a glucose-lactate analyzer (ABL700; Radiometer). Urinary output was recorded every hour.

Statistical Analysis

Baseline variables were compared with a Student *t* test. Kaplan-Meier curves were constructed for overall survival and compared by the log rank test. A two-way (time and group) analysis of variance with repeated measures taking into account missing values was used to make comparisons for other continuous parameters. If significant, each time point difference between group animals was compared with a *t* test with Bonferroni correction. Statistical analysis was performed using the JMP software package (JMP; SAS Institute Inc., Cary, NC). Data are expressed as mean ± SD. A *P* value less than 0.05 was considered statistically significant.

Results

There were no differences in body weight or other baseline parameters between the groups.

During the first 4 h, hemodynamic parameters, respiratory variables, blood lactate concentrations, and diuresis were similar in the two groups (table 1). In the group of animals treated without blood warming, body temper-

Table 1. Changes in Selected Variables over Time in the Two Groups of Sheep

		Time						
		Baseline		HF, 100 ml · kg^{-1} · h^{-1}				
	Group	1 h	3 h	5 h	7 h	9 h	11 h	13 h
Hemoglobin, g/dl	Without blood warming	10.9 ± 1.6	11.4 ± 1.2	11.6 ± 3.7	11.7 ± 3.3	11.2 ± 2.9	12.1 ± 3.0	10.3 ± 0.0
	With blood warming	9.9 ± 1.8	11.9 ± 2.8	10.7 ± 1.6	10.4 ± 1.7	10.6 ± 2.2	10.0 ± 2.2	10.5 ± 2.6
Heart rate, beats/min	Without blood warming	90 ± 43	91 ± 31	144 ± 30	174 ± 24	139 ± 26	146 ± 14	134 ± 0.0
	With blood warming	100 ± 27	97 ± 38	142 ± 64	143 ± 23	150 ± 17	152 ± 31	149 ± 25
PAOP, mmHg	Without blood warming	3.8 ± 2.3	6.2 ± 1.9	6.0 ± 2.2	5.8 ± 3.1	7.2 ± 3.3	8.5 ± 5.8	11.0 ± 1.4
	With blood warming	2.0 ± 1.0	1.8 ± 2.2*	1.0 ± 0.7*	4.8 ± 6.1	4.2 ± 3.8	6.2 ± 4.7	8.4 ± 4.9
RAP, mmHg	Without blood warming	0.0 ± 0.0	0.4 ± 0.6	0.0 ± 0.0	0.4 ± 0.9	2.0 ± 2.0	4.0 ± 4.1	6.0 ± 5.1
	With blood warming	0.3 ± 0.5	0.2 ± 0.5	0.0 ± 0.0	1.4 ± 3.1	1.4 ± 3.1	1.2 ± 1.6	1.2 ± 1.0
EVLW, ml	Without blood warming	463 ± 137	407 ± 109	362 ± 69	397 ± 125	361 ± 135	454 ± 183	362 ± 191
	With blood warming	592 ± 91	685 ± 294	427 ± 25	555 ± 169	516 ± 142	494 ± 162	519 ± 163
Pao_2/Fio_2	Without blood warming	191 ± 113	208 ± 111	249 ± 99	214 ± 66	211 ± 91	184 ± 59	192 ± 80
	With blood warming	159 ± 105	204 ± 113	227 ± 111	261 ± 85	269 ± 123	269 ± 158	227 ± 140
Oxygen delivery, ml/min	Without blood warming	424 ± 87	461 ± 108	467 ± 203	544 ± 209	512 ± 271	405 ± 165	286 ± 40
	With blood warming	500 ± 143	512 ± 104	529 ± 135	628 ± 179	684 ± 423	532 ± 233	509 ± 260
Oxygen uptake, ml/min	Without blood warming	103 ± 38	124 ± 40	141 ± 16	147 ± 28	132 ± 53	126 ± 43	136 ± 35
	With blood warming	131 ± 24	141 ± 22	126 ± 40	147 ± 23	155 ± 44	125 ± 37	156 ± 35
Oxygen extraction ratio, %	Without blood warming	24 ± 9	27 ± 8	34 ± 11	30 ± 12	29 ± 9	32 ± 2	48 ± 19
	With blood warming	28 ± 7	26 ± 4	24 ± 6	24 ± 5	25 ± 12	24 ± 13	30 ± 11
Svo_2, %	Without blood warming	70 ± 10	70 ± 12	65 ± 12	66 ± 15	63 ± 13	62 ± 6	47 ± 14
	With blood warming	64 ± 9	70 ± 10	72 ± 8	76 ± 7	76 ± 11	75 ± 11	69 ± 10
Reg CO_2, mmHg	Without blood warming	39 ± 5	35 ± 6	34 ± 6	37 ± 4	40 ± 8	42 ± 7	52 ± 0
	With blood warming	42 ± 8	45 ± 4	43 ± 3	44 ± 9	48 ± 16	46 ± 12	54 ± 8
Qmes, ml/min	Without blood warming	95 ± 55	128 ± 82	160 ± 86	131 ± 35	124 ± 107	83 ± 82	16 ± 23
	With blood warming	146 ± 54	93 ± 36	131 ± 45	160 ± 90	159 ± 102	122 ± 53	116 ± 63*

(*continued*)

ature decreased after initiation of hemofiltration and remained less than baseline until the end of the experiment, with a lowest value of 36.1°C (fig. 1). In the group with blood warming, body temperature remained at baseline levels during hemofiltration and thereafter increased significantly from baseline with a highest value of 40.8°C ($P < 0.05$; fig. 1).

In both groups, fluid resuscitation provoked a typical hyperdynamic septic shock manifest by a decreased mean arterial pressure and SVR, and increased cardiac output. However, in the group without blood warming, cardiac output, stroke volume, left ventricular stroke work, and mean arterial pressure were lower compared with values in the group with blood warming (figs. 2 and 3). SVR was similar in the two groups (fig. 3). Mesenteric blood flow decreased after 5 h and remained low in the group without blood warming (table 1).

Plasma bicarbonate and arterial pH (fig. 4) decreased during the experiment and were significantly lower in the group without blood warming ($P < 0.05$). Plasma lactate levels increased progressively to more than 10 mM in the group without blood warming, significantly higher than in the group with blood warming ($P < 0.05$). Urine output decreased progressively after 5 h to anuria in the group without blood warming. The survival time was significantly longer in the group with than in the group without blood warming ($P < 0.05$; fig. 5).

Discussion

The major finding of this study was that by preventing a decrease in body temperature during hemofiltration by using a blood warmer, the time to develop hypotension was prolonged, metabolic acidosis was attenuated, and survival was improved. After initial fluid resuscitation, human septic shock is characterized by a hyperdynamic state, with low arterial blood pressure, high cardiac output, and low SVR. This clinical picture is usually accompanied by high fever. In our sheep model, this situation is reproduced well by inducing peritonitis, followed by generous fluid administration.[15,19] The sheep develop a hyperdynamic pattern with increased cardiac index, decreased SVR, and lactic acidosis. Mortality is 100% at 24 h. The evolution to death is clearly related to multiple organ failure characterized by hypotension, oliguria, and respiratory failure.

Our study confirms previous findings that higher ultrafiltration rates in CVVH can easily decrease core body temperature.[5,6] This decrease is difficult to prevent without an additional warming system. The prevention of the decrease in temperature during hemofiltration is directly related to the ultrafiltration rate.[5]

The decrease in core temperature observed in our study worsened hemodynamic status, including a rapid development of hypotension and a decrease in cardiac

Table 1. Continued

		Time				
	Group	15 h	17 h	19 h	21 h	24 h
Hemoglobin, g/dl	With blood warming	10.8 ± 3.2	11.5 ± 3.5	10.7 ± 4.3	13.0 ± 0.9	13.1 ± 1.3
Heart rate, beats/min	With blood warming	150 ± 22	151 ± 11	178 ± 28	193 ± 25	203 ± 46
PAOP, mmHg	With blood warming	9.0 ± 6.7	8.0 ± 2.6	7.0 ± 2.8	8.0 ± 2.8	6.0 ± 0.0
RAP, mmHg	With blood warming	1.2 ± 1.3	2.7 ± 0.6	5.0 ± 0.9	7.0 ± 0.2	4.0 ± 02
EVLW, ml	With blood warming	534 ± 125	446 ± 151	296	302	408
Pao_2/Fio_2	With blood warming	198 ± 103	200 ± 135	224 ± 95	188 ± 137	174 ± 141
Oxygen delivery, ml/min	With blood warming	571 ± 290	668 ± 325	938 ± 322	776 ± 178	772 ± 236
Oxygen uptake, ml/min	With blood warming	165 ± 45	170 ± 57	172 ± 36	134 ± 13	156 ± 40
Oxygen extraction ratio, %	With blood warming	30 ± 10	28 ± 10	19 ± 3	18 ± 2	20 ± 0.7
Svo_2, %	With blood warming	68 ± 11	67 ± 13	77 ± 2	69 ± 10	79.5 ± 7.6
Reg CO_2, mmHg	With blood warming	50 ± 8	49 ± 11	44 ± 14	42 ± 9	46 ± 9
Qmes, ml/min	With blood warming	120 ± 42	99 ± 49	182 ± 21	154 ± 22	142 ± 16

There were 10 animals in each group. Data are shown as mean ± SD.

* $P < 0.05$ with blood warming *vs.* without.

EVLW = extravascular lung water; Fio_2 = inspired oxygen fraction; HF = hemofiltration; Pao_2 = arterial oxygen tension; PAOP = pulmonary artery occlusion pressure; Qmes = mesenteric arterial blood flow; RAP = right atrial pressure; Reg CO_2 = regional carbon dioxide from ileal loop; Svo_2 = mixed venous oxygen saturation.

output. Data regarding body temperature during hemofiltration are contradictory. Continuous hemofiltration-related hypothermia did not cause significant alternations in hemodynamic variables in critically ill patients with septic shock.[5,6] However, in a recent study in nine septic, mechanically ventilated patients,[19] cooling due to CVVH did result in significant decreases in heart rate, cardiac output, and systemic oxygen delivery and consumption, although in this study, acid–base balance remained unchanged. These discrepancies can be explained by two factors: First, in these studies, hemofiltration was used in septic patients who had already established a loss of vascular tone. In our sheep, however, CVVH was started early, even before the development of shock. In another study in the same model, we applied hemofiltration as an early intervention and compared it with control animals not receiving hemofiltration, only fluid resuscitation. We observed an increase in survival time in the hemofiltration group compared with the control group, despite the fact that temperature increased similarly in both groups (P. Rogiers *et al.*, Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium, unpublished data, 2005). Indeed, it has been shown by others that early hemofiltration has beneficial effects, whereas late application of hemofiltration is not useful in sepsis.[20] Second, we used an ultrafiltration rate of 100 ml · kg^{-1} · h^{-1} in our experiments, which is very high and which we used previously in two studies in canine endotoxic shock.[21,22]

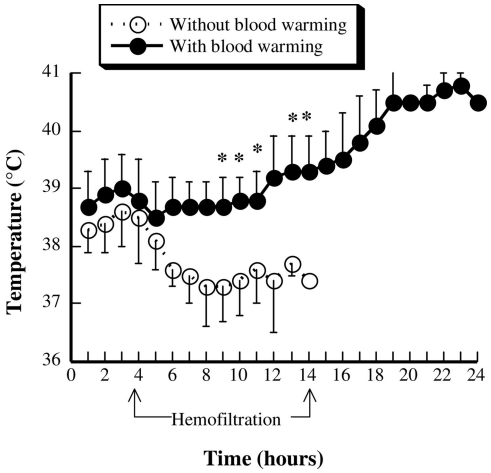

Fig. 1. Time course of core temperature (°C) in the two groups of animals. *Open circles* = without blood warming (n = 10); *filled circles* = with blood warming (n = 10). Data are shown as mean ± SD. * $P < 0.05$ between groups.

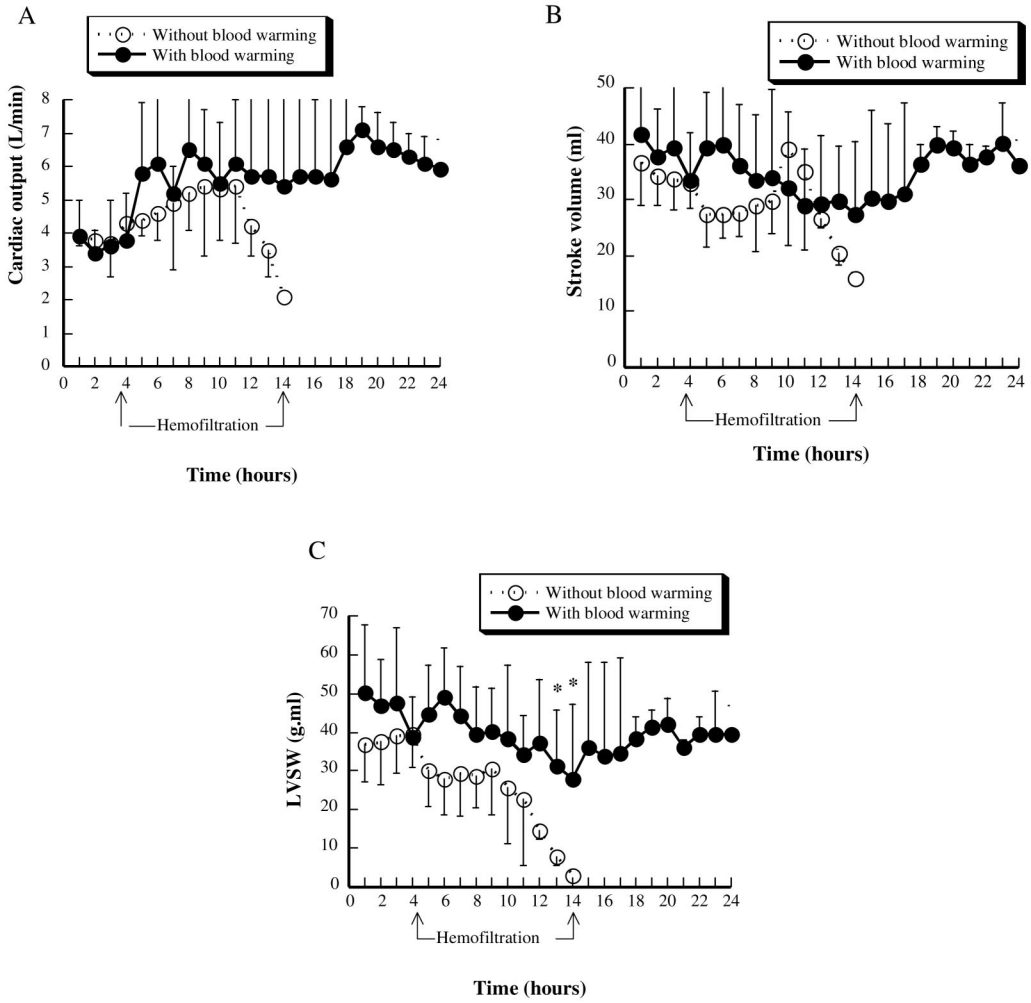

Fig. 2. Time course of cardiac output (*A*), stroke volume (*B*), and left ventricular stroke work (LVSW; *C*) in the two groups of animals. *Open circles* = without blood warming (n = 10); *filled circles* = with blood warming (n = 10). Data are shown as mean ± SD. * $P < 0.05$ between groups.

Our observations may be even more relevant if high ultrafiltration rates are applied in the future in patients. This ultrafiltration rate showed a higher cardiac index and better maintained arterial pressure than a lower ultrafiltration rate in a porcine pancreatitis model.[23,24]

Although we did not study the mechanisms involved in the differences observed, there are several possible reasons for the deleterious effects of decreasing body temperature in septic shock. First, temperature can decrease cardiac function as seen in our study. The microcirculation may also be impaired, resulting in worse tissue perfusion, blood lactate increase, and organ dysfunction. Second, lower body temperature also decreases the production of protective agents such as heat shock protein.[25] Even mild decreases in temperature can influence lymphocyte function, phagocytic activity, and cytokine production.[26,27] Indeed, laboratory animals subjected to hypothermia showed increased sensitivity to bacterial infections as compared with normothermic animals,[28,29] and septic shock patients with hypothermia have higher mortality rates than normothermic or febrile patients.[30]

In another study using the same sheep model as in the current study, we tested the effects of antipyretic therapy and external cooling to reduce fever.[10] In these sheep, the febrile response was associated with better respiratory function, lower blood lactate concentrations, and prolonged survival time; survival was shorter if the febrile response was neutralized.

Although this model is designed to mimic human sepsis, care must be taken when extrapolating these animal data to humans; our model mainly reflects the hemodynamic alterations that occur in septic shock. Other investigators have also used sheep to investigate various aspects of hemorrhagic shock and sepsis.[31–35] Our study has several limitations, including that we did not give antibiotics or vasopressors so as to avoid any more variables. Second, the animals were initially healthy, which is different from the clinical situation where patients often have several comorbidities and cardiorespiratory compromise. Third, we did not measure cytokine levels, because there are few cytokine assays available for use in sheep.

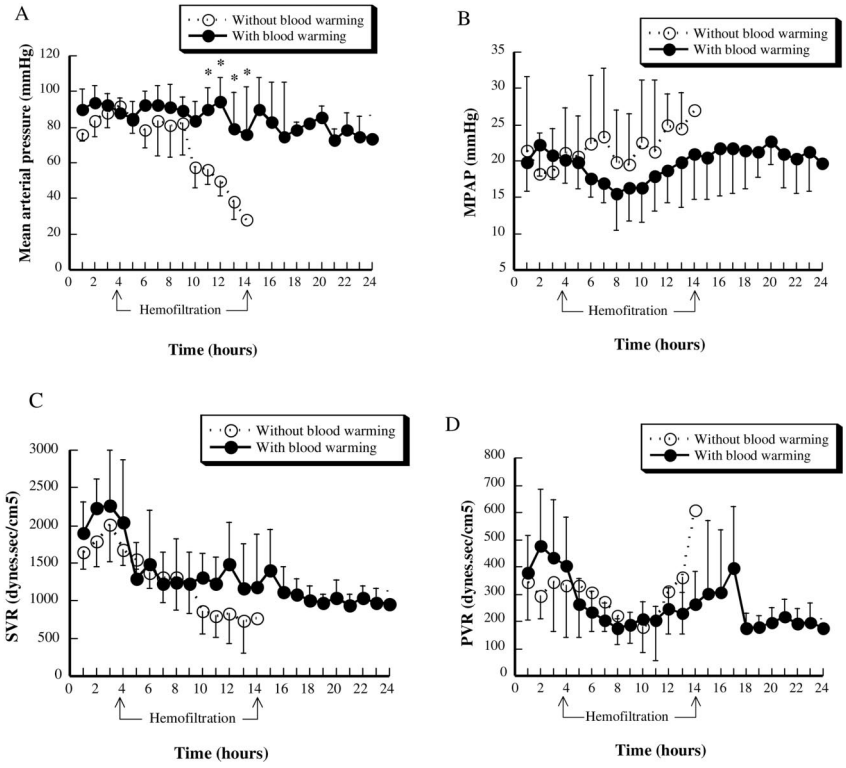

Fig. 3. Time course of mean arterial pressure (*A*), mean pulmonary artery pressure (MPAP; *B*), systemic vascular resistance (SVR; *C*), and pulmonary vascular resistance (PVR; *D*) in the two groups of animals. *Open circles* = without blood warming (n = 10); *filled circles* = with blood warming (n = 10). Data are shown as mean ± SD. * $P < 0.05$ between groups.

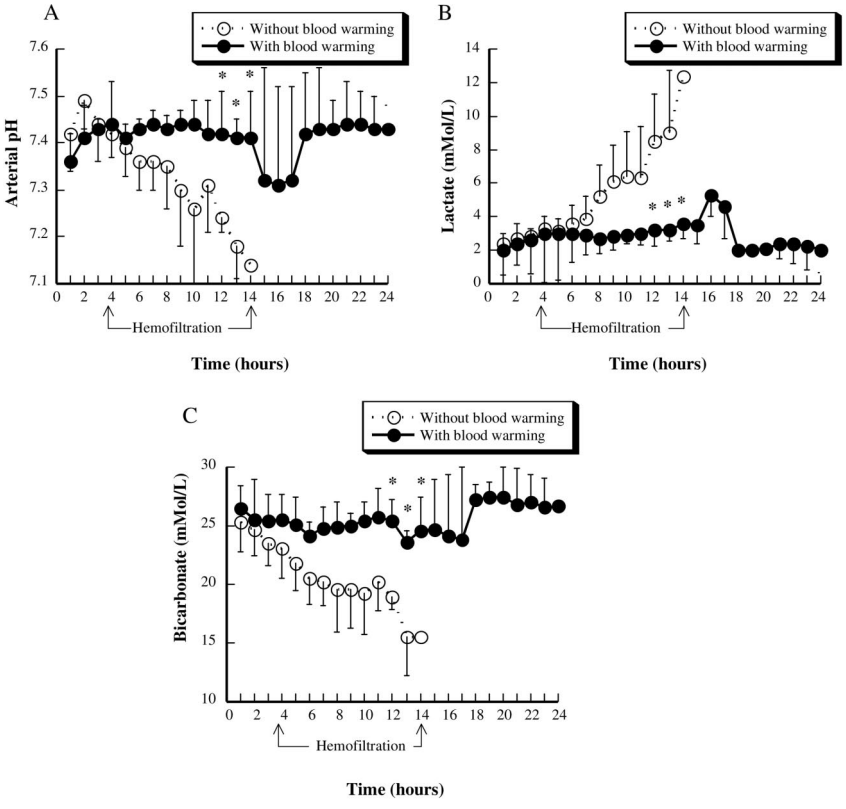

Fig. 4. Time course of arterial pH (*A*), lactate (*B*), and bicarbonate (*C*) in the two groups of animals. * $P < 0.05$ at that time point between groups. *Open circles* = without blood warming (n = 10); *filled circles* = with blood warming (n = 10). Data are shown as mean ± SD. * $P < 0.05$ between groups.

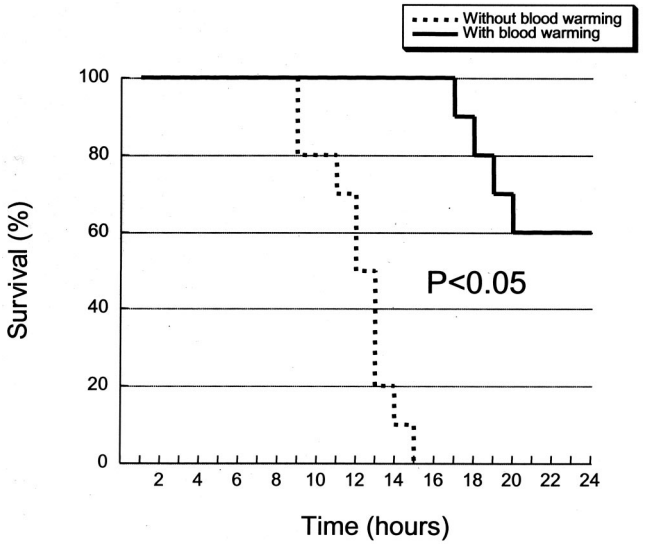

Fig. 5. Kaplan-Meier survival curve in the two groups of animals. *Dotted line* = without blood warming (n = 10); *solid line* = with blood warming (n = 10).

In conclusion, in this ovine septic shock model, hemofiltration with a blood warming system prevented the temperature decrease associated with hemofiltration and improved hemodynamics and lactic acidosis, resulting in increased 24-h survival. These observations stress the importance of temperature control and suggest that blood warming during hemofiltration is important in septic shock. Clinical studies are needed to confirm these experimental data.

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