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FEVER CONTROL IN SEPTIC SHOCK: BENEFICIAL OR HARMFUL?

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ABSTRACT—The beneficial effects of interventions to control fever in sepsis are controversial. We investigated whether the use of acetaminophen and external cooling is beneficial to control fever in septic shock. We studied 24 fasted, anesthetized, invasively monitored, mechanically ventilated female sheep (27.0 ± 4.6 kg) that received 0.5 g/kg body weight of feces into the abdominal cavity to induce sepsis. Ringer's lactate (RL) was titrated to maintain pulmonary artery occlusion pressure (PAOP) at baseline levels throughout the experimental period. During the 2 h after the surgical operation, animals were placed in the hypothermia group if their temperature fell below 36.0°C; the other animals were randomized to three groups: high fever (T > 39.0°C), mild fever (37.5°C < T < 38.5°C), and normothermia (36.0°C < T < 37.0°C). The administration of 25 mg/kg acetaminophen every 4 to 6 h combined with external cooling (ice pad) was used to control core temperature in these three groups. The PaO_2/FiO_2 ratio was higher and blood lactate concentration was lower in the high fever than in the other groups ($P < 0.01$ and 0.05, respectively). Survival time was longer in the high fever group (25.2 ± 3.0 h) than in the mild fever (17.7 ± 3.5 h), normothermia (16.0 ± 1.9 h), and hypothermia (18.5 ± 2.5 h) groups ($P < 0.05$ for all). Plasma heat shock protein (HSP) 70 levels were higher in the two fever groups than in the other groups ($P < 0.05$). In this clinically relevant septic shock model, the febrile response thus resulted in better respiratory function, lower blood lactate concentration, and prolonged survival time. Antipyretic interventions including acetaminophen and external cooling were associated with lower circulating HSP70 levels. These data challenge the temperature control practices often used routinely in acutely ill patients.

KEYWORDS—Acetaminophen, fever, heat shock proteins, cooling, sepsis

INTRODUCTION

As a temporary resetting of the body's thermostatic setting point, fever is regarded as a fundamental component of the acute-phase response to infection. Indeed, fever has been conserved through evolution in many species (1).

Despite considerable research in this field, whether fever is globally beneficial or harmful remains unclear. Known beneficial effects of fever include impaired bacterial growth (2), reduced virus replication, and enhanced host response by increasing leukocyte activity, natural killer cell activity (3), T cell activation, and mononuclear cell production of cytokines (4, 5). Fever also decreases the affinity of hemoglobin for oxygen, which may facilitate oxygen delivery to the tissues. At the same time, fever increases tissue oxygen requirements, and this may be poorly tolerated in patients with compromised cardiopulmonary function; it also causes patient discomfort, and may worsen central nervous system damage (6). Fever has been shown to enhance the effects of endotoxin in some models (7), and to attenuate them in others (8).

No prospective, randomized clinical trial has convincingly assessed the effects of antipyretic measures in humans. Experimental studies have yielded controversial results, but the experimental conditions used limit interpretation of these results and applicability to the clinical arena: the temperatures attained in many experimental models (with external heat) have frequently exceeded the physiologic febrile range during infection, and thus have no physiologic relevance. Some models using endotoxin challenge may not be clinically relevant (9). For example, rodents may not be suitable for studying fever, as mice lacking the neuronal prostaglandin E2 (PGE2) receptor subtype EP3 (cellular receptors for PGE2) have an impaired febrile response to pyrogens (10).

We have developed a ewe septic shock model induced by acute peritonitis (11) that avoids some of the above shortcomings. We have observed that, as in humans, the majority of animals develop high fever, whereas a small proportion develop hypothermia. With this model, we investigated whether fever has beneficial effects in septic shock.

MATERIALS AND METHODS

Experimental animals

The study protocol was approved by the Free University of Brussels' laboratory animal utilization committee. Twenty-four female sheep (27 ± 4.6 kg) were used. They were fasted for 24 h before the study with free access to water.

Anesthesia and surgical procedure

On the day of experiment, the animals were anesthetized with 75 μg/kg intramuscular xylazine hydrochloride and 6 mg/kg ketamine hydrochloride, and they were weighed and placed in a supine position. A peripheral venous 18G catheter (Surflo IV catheter, Terumo, Haasrode, Belgium) was introduced into a surface vein on one of the front legs. After endotracheal intubation (tracheal tube, 7.5–8.0, Hi-Contour; Mallinckrodt Medical, Athlone, Ireland), mechanical ventilation (Servo ventilator 900 C; Siemens-Elema, Solna, Sweden) was started with the following parameters: respiratory rate = 18/min, tidal volume (Vt) = 9 mL/kg, PEEP = 10 cmH_2O, FiO2 = 100%, inspiratory time/expiratory time (I/E) = 1:2, square wave pattern. A 4-mL bolus of pancuronium bromide was given immediately after the endotracheal intubation and was maintained at a dose of 50 μg/kg/h thereafter. Anesthesia was maintained with 0.2 mg/kg/h i.v. midazolam and 3 μg/kg/h fentanyl. Ringer's lactate (RL) was initially infused at 20 mL/kg/h.

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Surgical procedures

The right femoral vein and right femoral artery were surgically exposed. An arterial catheter (5F Introducer, Vygon, Ecouen, France) was introduced in the femoral artery. A 7F Swan-Ganz catheter (Edwards Life Sciences, Irvine, CA) was introduced through the right femoral vein and vena cava into the pulmonary artery. Pulmonary artery occlusion pressure (PAOP) was measured at baseline. A midline laparotomy was performed. An opening of 1 cm was made in the cecum and 0.5 g/kg body weight of its content was spilled into the abdominal cavity. The cecotomy and abdomen were then sutured in two layers. A Foley catheter (14F; Folatex, Mentor, Le Plessis Robinson, France) was introduced to measure urine output.

After the surgical preparation, animals were turned prone and, for 2 h, the core temperature was continuously observed. For sheep, the normal range of body temperature is 38.0°C to 39.0°C. We have observed a progressive decrease in body temperature of around 2°C during the first 2 h due to general anesthesia (12) and the abundant RL infusion at room temperature. Therefore, we considered a core temperature of 36°C to 37°C as normal at the end of surgery and defined high fever as temperature >39.0°C, mild fever as temperature between 37.5°C to 38.5°C, and hypothermia as a temperature less than 36.0°C. Therefore, randomization was performed as follows: 2 h after the surgical operation, if the temperature was <36.0°C, the animal was considered spontaneously hypothermic, and no effort was made to raise this temperature; the other animals were randomized to three groups: high fever (T > 39.0°C), mild fever (37.5°C < T < 38.5°C), and normothermia (36°C < T < 37°C). The high fever group received no intervention, whereas in the two other groups, temperature was maintained within each defined range with the administration of 25 mg/kg acetaminophen every 4 to 6 h combined with external body cooling (ice pads) when necessary; if the temperature decreased out of range, a fluid warmer (HL-90 Level One Technologies, Rockland, MA) was used to raise core temperature.

Minute volume, plateau pressure, peak inspiratory pressure, and inspiratory tidal volume and expiratory tidal volume were recorded every 60 min. A PEEP of 10 cmH_2O, plateau pressure at 10% inspiratory time, I:E = 1:2, and a square wave pattern were maintained during the whole experiment in all groups. FiO_2 was adjusted to maintain PaO_2 between 80 and 140 mmHg. RR was adjusted to maintain $PaCO_2$ between 35 and 45 mmHg. RR was not increased when peak inspiratory pressure (PIP) reached 50 cmH_2O.

All intravascular pressures, including mean arterial pressure (MAP), pulmonary arterial pressure (PAP), central venous pressure (CVP) and PAOP measurements, were referenced to midchest level and were recorded from calibrated pressure transducers (Sirecust 404; Siemens, Erlangen, Germany), and values were obtained at end expiration. Heart rate (HR), core temperature (T), and cardiac output (CO) were continuously monitored (Vigilance Baxter, Edwards Lifesciences, Irvine, CA) and recorded every 60 min. After baseline measurement, RL was titrated to maintain PAOP at baseline levels. The following derived variables were calculated using standard formulas: stroke volume (SV; L/min/beat), cardiac index (CI; L min^{-1} m^{-2}), systemic vascular resistance (SVR; dyne/s/cm^{-5}), pulmonary vascular resistance (PVR; dyne/s/cm^{-5}), oxygen delivery (DO_2; mL/kg/min), oxygen consumption (VO_2; mL/kg/min), and oxygen extraction (O_2ER). The indexed variables were calculated using the animal's weight. Arterial and mixed venous blood was sampled in heparinized syringes for immediate blood gas analysis (ABL500 OSM3 Radiometer, Copenhagen, Denmark). Hemoglobin concentration and oxygen saturations were measured with analyzer adapted to sheep (OSM3 Radiometer).

Post mortem studies

Specimens of lung, heart, liver, kidney, spleen, and small intestine were taken immediately after each sheep's death. Samples were divided into two parts: one part was saved in 4% buffered formalin, routinely processed into paraffin blocks, sectioned at 4 μm, and stained with hematoxylin and eosin (HE). A pathologist blinded to the study protocol examined histology. The other part was saved in liquid nitrogen for heat shock protein (HSP) measurement.

HSP measurements

Arterial blood samples were taken at T-1 after cannulating the femoral arterial catheter, and at T0 when the sheep was turned back from the supine to the prone position, and then at 1, 4, 5, 9, 13, 17, and 21 h until the sheep died. Three milliliters of blood was injected into the EDTA (K_2) tube (VenojectII; Terumo European, Leuven, Belgium) and saved on ice. After centrifugation at 3000 r/min for 10 min at 4°C, plasma was separated to an Eppendorf tube (Sigma-Aldrich, Brussels, Belgium) and stored at –70°C for future measurements. HSP70 levels in the plasma and tissues were measured using enzyme-linked immunoabsorbant assay (ELISA; StressGen Biotechnologies, Victoria, British Columbia, Canada).

Tissue HSP70 measurements: 0.5 cm^3 of frozen tissue was ground and dissolved in 1 mL of HSP70 extraction solution (containing protease inhibitors), homogenized, and centrifuged at 21,000*g* for 10 min at 4°C. The supernatant collected was the tissue extract, which was placed in a polypropylene tube and refrigerated at −30°C for later HSP70 concentration. Coomassie Blue binding was performed to decide total protein concentration. Tissue extract HSP70 concentration was measured by ELISA following the manufacturer's protocol and was calibrated with total protein concentration.

Statistical analysis

Data are expressed as mean ± SD, unless stated otherwise. A one-way analysis of variance (ANOVA) for repeated measurements (SPSS, Chicago, IL) was used to compare variables in the different groups. A two-way ANOVA for repeated measurements followed by a modified *T* test was used for time-related variables among groups. A P value <0.05 was considered significant.

RESULTS

There was no significant difference in sheep weight among the four groups (29.5 ± 4.6 kg in the high fever group, 26.9 ± 4.3 kg in the mild fever group, 27.3 ± 3.4 kg in the normothermia group, and 24.2 ± 5.3 kg in the hypothermia group, $P > 0.05$). Differences in core temperatures were highly significant ($P < 0.0001$, Fig. 1). There were no significant differences in hemodynamic parameters between the groups (Table 1), except that DO_2 was higher in the two fever groups than in the other groups ($P < 0.05$, Fig. 1). Oxygen consumption was lower in the hypothermia group than in the other groups, but the differences did not reach statistical significance.

Interestingly, the PaO_2/FiO_2 ratio increased considerably in the spontaneously hypothermic group during the first hours of the experiment, to decrease thereafter at a much more rapid pace than in the other groups ($P < 0.001$, Fig. 1). Toward the end of the experiment, the febrile groups had a higher PaO_2/FiO_2 than the other groups.

Blood arterial lactate concentrations were higher in the hypothermic group than in the other groups ($P < 0.05$, Fig. 1).

HSP70 levels

Blood HSP70 concentrations increased significantly in all groups, but especially in the two fever groups ($P < 0.05$, Fig. 2). Because all the animals were not sacrificed at the same time point, we did not compare the tissue HSP concentrations among groups. In all groups, tissue HSP concentration was higher in the lung than in the heart, liver, spleen, kidney, or small intestine ($P < 0.05$, Fig. 3).

Survival time

Survival time was longer in the high fever group (25.2 ± 3.0 h) than in the mild fever group (17.7 ± 3.5 h), normothermia group (16.0 ± 1.9 h), and hypothermia group (18.5 ± 2.5 h; $P < 0.05$, Fig. 4). Pathologic findings were similar in the four groups.

DISCUSSION

The present study used a clinically relevant model of polybacterial peritonitis in anesthetized animals. The main findings were that animals that developed fever had higher DO_2, lower lactate concentration, better gas exchange, and longer survival time than animals receiving acetaminophen and external cooling to maintain temperature within the normal range.

Despite many studies, the need to control fever remains a topic of controversy. Polythermic animals infected by subcutaneous inoculation with gram-negative bacterial pathogens have a higher survival rate when placed in a warmer environment (13), and some studies on the use of antipyretic agents

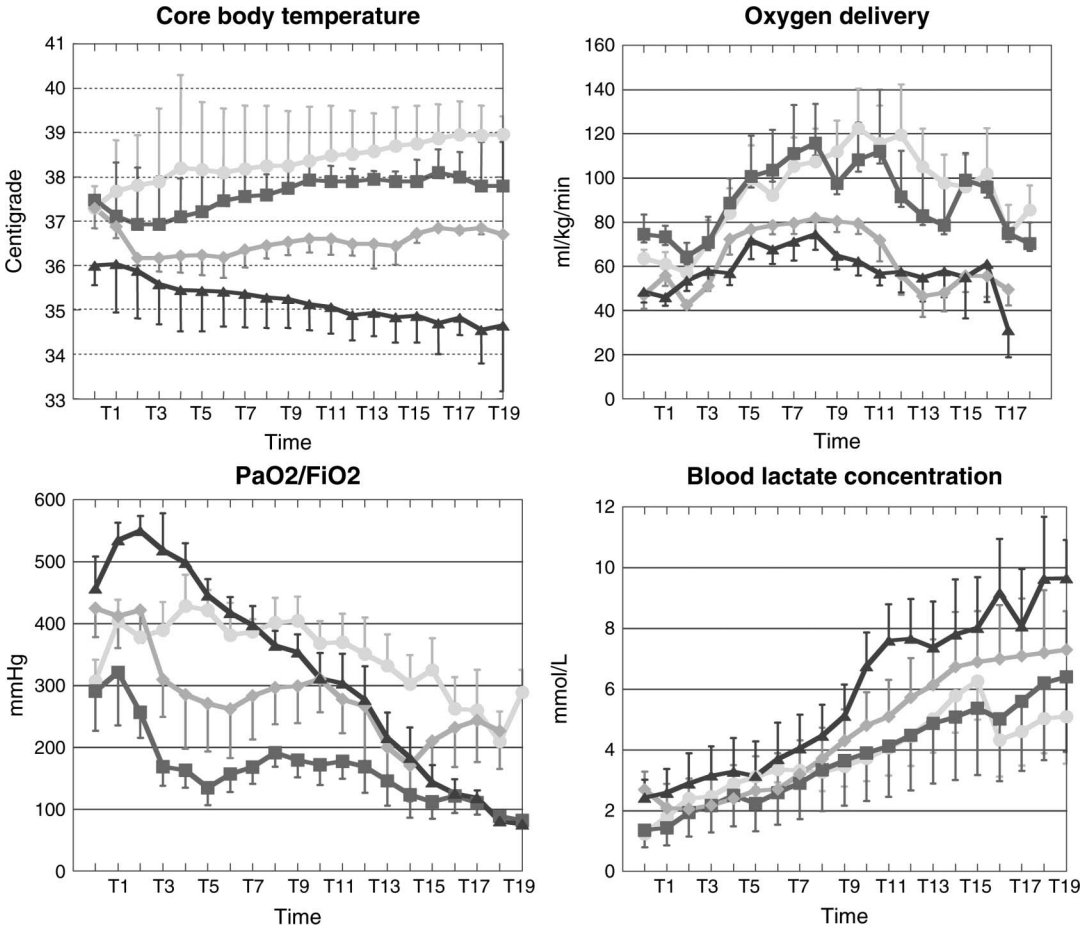

Fig. 1. **Core temperature, oxygen delivery, PaO_2/FiO_2 ratio, and arterial blood lactate concentration in the different groups.** ●, T > 39.0°C; ■, 37.5°C < T < 38.5°C; ◆, 36.0°C < T < 37.0°C; ▲, T < 36.0°C. Data are expressed as mean ± SEM.

in larger animals have suggested they may be harmful (14, 15). Indeed, from the preantibiotic era there are abundant data, although often uncontrolled, on the deliberate use of elevated body temperature to treat infections. The beneficial effects of hot baths and malarial fevers in syphilis were noted as early as the 15th century (16). Some retrospective studies have suggested that fever may be associated with improved survival and shortened disease in patients with spontaneous bacterial peritonitis (17, 18), polymicrobial sepsis (2), *Escherichia coli* bacteremia (19), and *Pseudomonas aeruginosa* sepsis (20). However, fever has also been shown to have harmful effects in some animal models (21), and administration of acetaminophen was an independent predictor of survival in patients infected with *E. coli* and *P. aeruginosa* (19, 20).

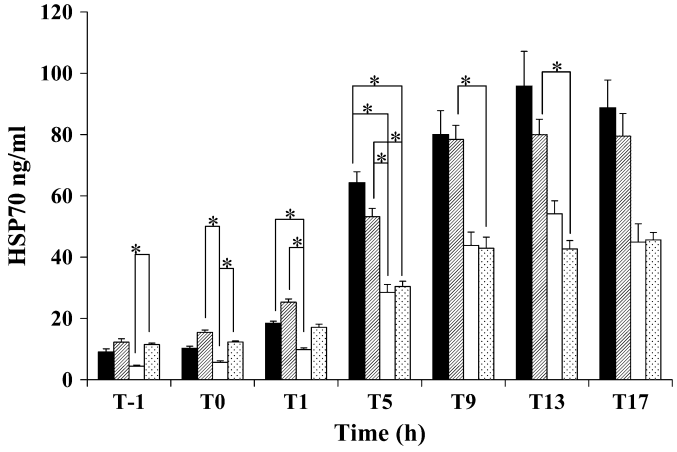

Fig. 2. **Plasma HSP70 levels in the different groups (an asterisk represents a statistically significant difference).** Black column, >39.0°C; hatched column, 37.5°C < T < 38.5°C; black points, 36.0°C < T < 37.0°C; empty column, < 36.0°C. Data are expressed as mean ± SE.

An interesting finding was the transient improvement in gas exchange in the hypothermic group, followed by a dramatic deterioration. This observation may help to reconcile previous discrepancies about the effects of temperature on lung function. Indeed, some short-term studies have indicated that hypothermia may exert protective effects early in acute respiratory failure, whereas others have shown hyperthermia with HSP expression to be associated with better lung function. Akinci et al. (22) demonstrated that hypothermia (31°C-32°C) had a protective effect on lungs and reduced the risk of ventilator-induced lung injury (VILI) in the rat. Suzuki et al. (23) showed that increased temperature (41°C) accentuated edema formation in intact rabbits and in isolated perfused lungs subjected to injurious ventilation compared with temperatures of 33°C. These two experiments did not reveal any protective effects of hyperthermia; the reason for this was probably, as suggested by the authors, that HSP70 secretion did not reach its peak because the observation time was too short. However, Koh et al. (24) observed that transient whole-body hyperthermia (>40°C for 13 min 18 h before LPS administration) reduced lung damage in a mice endotoxemia model. Villar et al. (25) showed that

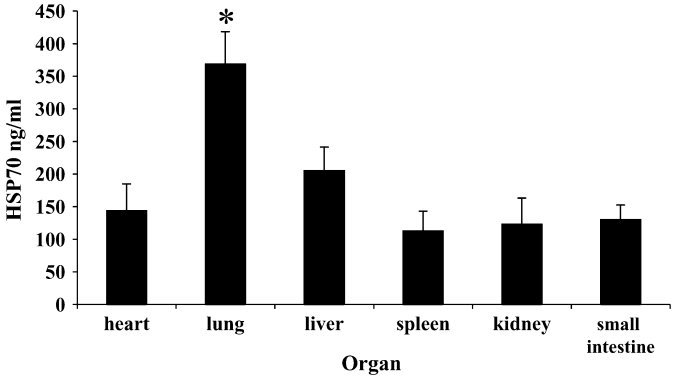

FIG. 3. **Different organ HSP70 concentrations (an asterisk represents a statistically significant difference comparing lung tissues with other tissue) in all animals.**

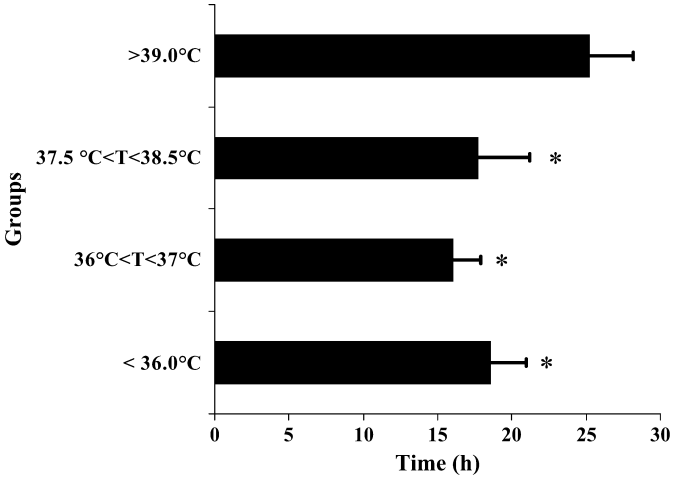

FIG. 4. **Survival time in different groups (an asterisk represents a statistically significant difference when comparing the hyperthermia group with other groups).**

thermal pretreatment (15 min at 41°C–42°C 18 h before cecal ligation and puncture) reduced lung damage and mortality rates in an acute lung injury model. The same group of investigators also showed that induction of HSP72 expression in the lungs by administration of sodium arsenite conferred transient protection against experimental sepsis (26). Furthermore, restoring the expression of HSP70 using adenovirus gene therapy attenuated interstitial and alveolar edema and protein exudation and neutrophil accumulation in a cecal ligation and puncture-induced model of acute respiratory distress syndrome (27). In our study, fever was associated with higher HSP70 concentrations and all animals had increased HSP70 blood concentrations as a result of the septic injury. In addition, the fever group eventually had a higher PaO_2/FiO_2 ratio at the time HSP70 concentrations in the lung were highest. Acetaminophen and external body cooling were associated with lower HSP levels in the blood. Previous experimental studies have indicated that HSP may have anti-inflammatory effects, reducing levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and also IL-10 (28), and the harmful effects of antifebrile interventions may be, at least in part, mediated by lower HSP70 availability. This is an interesting field of ongoing research.

Despite anticipated higher DO_2, there was no significant difference in VO_2 between the various groups, probably because of the short-term nature of our study. However, blood lactate concentrations were lower in the hyperthermia groups, suggesting improved cellular metabolism. This is in contrast to what one may expect, and may have resulted from higher DO_2 in the presence of a nonsignificant difference in VO_2. Bernard et al. (29) suggested in a subgroup of patients that the administration of ibuprofen could result in lower blood lactate concentrations.

About one-fourth of the animals were spontaneously hypothermic. These animals had higher blood lactate concentrations and a poorer outcome. Similar observations have been made in humans, where 13% to 25% of patients with sepsis had hypothermia and this was associated with an increased mortality (29–33). Hypothermia is known to reduce host immune response and increase the incidence of infectious complications (34). Uncontrolled studies have reported an association of increased mortality with the absence of fever in polymicrobial or gram-negative sepsis, in patients with pneumococcal meningitis, and in elderly patients with community-acquired pneumonia (35–38).

Human studies have not clearly defined whether fever should be controlled or not (39, 40). We used an experimental model that mimics clinical sepsis and septic shock. However, our study has a number of limitations. First, although the model

TABLE 1. **MAP, MPAP, and PAOP in the different groups of animals (mean ± SD)**

Group	T-1	T0	T1	T5	T9	T13	T17	T21
MAP (mmHg)								
>39.0°C	115 ± 20	104 ± 15	105 ± 24	116 ± 14	110 ± 13	111 ± 18	96 ± 29	84 ± 37
37.5 < T < 38.5°C	108 ± 18	106 ± 9	89 ± 8	110 ± 12	110 ± 14	98 ± 30	119 ± 22	–
36.0 < T < 37.0	105 ± 10	91 ± 9	77 ± 6	106 ± 22	104 ± 24	96 ± 37	81 ± 15	–
<36.0°C	99 ± 17	101 ± 11	91 ± 19	95 ± 14	101 ± 13	79 ± 29	72 ± 32	–
MPAP (mmHg)								
>39.0°C	23 ± 4	24 ± 7	25 ± 6	24 ± 6	22 ± 6	26 ± 5	31 ± 5	36 ± 11
37.5 < T < 38.5°C	19 ± 7	31 ± 11	26 ± 5	31 ± 8	28 ± 6	35 ± 6	48 ± 7	–
36.0 < T < 37.0	18 ± 3	32 ± 10	27 ± 7	29 ± 6	28 ± 12	32 ± 15	30 ± 12	–
<36.0°C	18 ± 5	27 ± 9	21 ± 4	21 ± 7	24 ± 4	38 ± 11	47 ± 6	–
PAOP (mmHg)								
>39.0°C	7 ± 1	6 ± 3	6 ± 3	4 ± 3	4 ± 3	6 ± 4	7 ± 4	8 ± 4
37.5 < T < 38.5°C	7 ± 1	7 ± 3	5 ± 2	5 ± 3	6 ± 3	5 ± 2	7 ± 2	–
36.0 < T < 37.0	6 ± 1	6 ± 1	6 ± 2	5 ± 2	5 ± 3	6 ± 3	6 ± 2	–
<36.0°C	6 ± 1	6 ± 2	6 ± 2	3 ± 3	3 ± 3	7 ± 4	9 ± 4	–

No significant difference was found between groups.

reproduces well the hemodynamic alterations of human septic shock, the animals were initially healthy and their response may be different from acutely ill patients with compromised cardiorespiratory reserve. Second, unlike the clinical situation, we chose not to give antibiotics or vasoactive agents to avoid the influence of these additional variables and to obtain a lethal model. Third, antipyretic agents may have their own side effects. Acetaminophen is regarded generally as a safe antipyretic drug, although it can alter liver function. It is unlikely that acetaminophen at the doses used (25 mg/kg every 4–6 h) would have had side effects in our short-term study. Fourth, the administration of muscle relaxants was necessary to prevent shivering, and this, along with the anesthetic agents, may also have influenced the febrile response and/or the effects of the antipyretic strategies. Finally, it is possible that other antipyretic strategies may have yielded different results.

In summary, in this septic shock model, antipyretic interventions, including acetaminophen and external cooling, were associated with lower circulating HSP70 concentrations, with harmful effects on respiratory function, with higher blood lactate concentrations, and with shortened survival times. Although, due to the limitations discussed above, we cannot directly extrapolate our experimental results to the clinical situation, our observations do suggest that the routine administration of antipyretic treatment may not be warranted in all critically ill patients. The time has come to conduct a randomized controlled trial to address this fundamental question.

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REFERENCES

1. Kluger MJ, Kozak W, Conn CA, Leon LR, Soszynski D: The adaptive value of fever. *Infect Dis Clin North Am* 10:1–20, 1996.
2. Mackowiak PA: Direct effects of hyperthermia on pathogenic microorganisms: teleologic implications with regard to fever. *Rev Infect Dis* 3:508–520, 1981.
3. Rowsey PJ: Pathophysiology of fever. Part 2: relooking at cooling interventions. *Dimens Crit Care Nurs* 16:251–256, 1997.
4. Jampel HD, Duff GW, Gershon RK, Atkins E, Durum SK: Fever and immunoregulation. III. Hyperthermia augments the primary in vitro humoral immune response. *J Exp Med* 157:1229–1238, 1983.
5. Roberts NJ Jr, Sandberg K: Hyperthermia and human leukocyte function. II. Enhanced production of and response to leukocyte migration inhibition factor (LIF). *J Immunol* 122:1990–1993, 1979.
6. Ginsberg MD, Busto R: Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke* 29:529–534, 1998.
7. Atwood RP, Kass EH: Relationship of body temperature to the lethal action of bacterial endotoxin. *J Clin Invest* 43:151–169, 1964.
8. Suganuma T, Irie K, Fujii E, Yoshioka T, Muraki T: Effect of heat stress on lipopolysaccharide-induced vascular permeability change in mice. *J Pharmacol Exp Ther* 303:656–663, 2002.
9. Romanovsky AA, Kulchitsky VA, Simons CT, Sugimoto N: Methodology of fever research: why are polyphasic fevers often thought to be biphasic? *Am J Physiol* 275:R332–R338, 1998.
10. Ushikubi F, Segi E, Sugimoto Y, Murata T, Matsuoka T, Kobayashi T, Hizaki H, Tuboi K, Katsuyama M, Ichikawa A, Tanaka T, Yoshida N, Narumiya S: Impaired febrile response in mice lacking the prostaglandin E receptor subtype EP3. *Nature* 395:281–284, 1998.
11. Sun Q, Dimopoulos G, Nguyen DN, Tu Z, Nagy N, Hoang AD, Rogiers P, De Backer D, Vincent JL: Low-dose vasopressin in the treatment of septic shock in sheep. *Am J Respir Crit Care Med* 168:481–486, 2003.
12. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C: Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 82:662–673, 1995.
13. Kluger MJ, Ringler DH, Anver MR: Fever and survival. *Science* 188:166–168, 1975.
14. Kurosawa S, Kobune F, Okuyama K, Sugiura A: Effects of antipyretics in rinderpest virus infection in rabbits. *J Infect Dis* 155:991–997, 1987.
15. Dwinger RH, Vos J, Nieuwenhuijs J, Zwart D, van Miert AS: Studies on the influence of non-steroidal anti-inflammatory drugs upon trypanosomiasis in goats and sheep. *J Vet Pharmacol Ther* 7:293–301, 1984.
16. Dennie CC: A History of Syphilis. Springfield, IL: Thomas, 1962.
17. Hoefs JC, Canawati HN, Sapico FL, Hopkins RR, Weiner J, Montgomerie JZ: Spontaneous bacterial peritonitis. *Hepatology* 2:399–407, 1982.
18. Weinstein MP, Iannini PB, Stratton CW, Eickhoff TC: Spontaneous bacterial peritonitis. A review of 28 cases with emphasis on improved survival and factors influencing prognosis. *Am J Med* 64:592–598, 1978.
19. Kuikka A, Sivonen A, Emelianova A, Valtonen VV: Prognostic factors associated with improved outcome of *Escherichia coli* bacteremia in a Finnish university hospital. *Eur J Clin Microbiol Infect Dis* 16:125–134, 1997.
20. Kuikka A, Valtonen VV: Factors associated with improved outcome of *Pseudomonas aeruginosa* bacteremia in a Finnish university hospital. *Eur J Clin Microbiol Infect Dis* 17:701–708, 1998.
21. Klastersky J: Experimental and clinical study of the favorable and unfavorable effects of fever and corticoid administration in bacterial infections. *Acta Clin Belg* 26(suppl 6):1–84, 1971.
22. Akinci IO, Cakar N, Tugrul S, Ozcan PE, Yilmazbayhan D, Celik M, Esen F, Telci L: Effect of hypothermia on ventilation-induced lung injury. *Intensive Care Med* 28:S62, 2002.
23. Suzuki S, Hotchkiss JR, Takahashi T, Olson D, Adams AB, Marini JJ: Effect of core body temperature on ventilator-induced lung injury. *Crit Care Med* 32: 144–149, 2004.
24. Koh Y, Lim CM, Kim MJ, Shim TS, Lee SD, Kim WS, Kim DS, Kim WD: Heat shock response decreases endotoxin-induced acute lung injury in rats. *Respirology* 4:325–330, 1999.
25. Villar J, Ribeiro SP, Mullen JB, Kuliszewski M, Post M, Slutsky AS: Induction of the heat shock response reduces mortality rate and organ damage in a sepsis-induced acute lung injury model. *Crit Care Med* 22:914–921, 1994.
26. Ribeiro SP, Villar J, Downey GP, Edelson JD, Slutsky AS: Sodium arsenite induces heat shock protein-72 kilodalton expression in the lungs and protects rats against sepsis. *Crit Care Med* 22:922–929, 1994.
27. Weiss YG, Maloyan A, Tazelaar J, Raj N, Deutschman CS: Adenoviral transfer of HSP-70 into pulmonary epithelium ameliorates experimental acute respiratory distress syndrome. *J Clin Invest* 110:801–806, 2002.
28. Flohe S, Dominguez FE, Ackermann M, Hirsch T, Borgermann J, Schade FU: Endotoxin tolerance in rats: expression of TNF-α, IL-6, IL-10, VCAM-1 and HSP 70 in lung and liver during endotoxin shock. *Cytokine* 11:796–804, 1999.
29. Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, Higgins SB, Swindell BB: The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med* 336:912–918, 1997.
30. Clemmer TP, Fisher CJ, Bone RC, Slotman GJ, Metz GA, Thomas FO: Hypothermia in the sepsis syndrome and clinical outcome. *Crit Care Med* 20:1395–1401, 1992.
31. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson W, Wright P, Dupont WD, Swindell BB: Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med* 27:699–707, 1999.
32. Peres-Bota D, Lopes-Ferreira F, Melot C, Vincent JL: Body temperature alterations in the critically ill. *Intensive Care Med* 30:811–816, 2004.
33. The veterans administration systemic sepsis cooperative study group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med* 317:659–665, 1987.
34. Russwurm S, Stonans I, Schwerter K, Stonane E, Meissner W, Reinhart K: Direct influence of mild hypothermia on cytokine expression and release in cultures of human peripheral blood mononuclear cells. *J Interferon Cytokine Res* 22:215–221, 2002.
35. Mackowiak PA, Browne RH, Southern PM Jr, Smith JW: Polymicrobial sepsis: an analysis of 184 cases using log linear models. *Am J Med Sci* 280:73–80, 1980.
36. Ahkee S, Srinath L, Ramirez J: Community-acquired pneumonia in the elderly: association of mortality with lack of fever and leukocytosis. *South Med J* 90:296–298, 1997.
37. Bryant RE, Hood AF, Hood CE, Koenig MG: Factors affecting mortality of gram-negative rod bacteremia. *Arch Intern Med* 127:120–128, 1971.
38. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 68:344–355, 1980.
39. Poblete B, Romand JA, Pichard C, Konig P, Suter PM: Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients. *Br J Anaesth* 78:123–127, 1997.
40. Gozzoli V, Schottker P, Suter PM, Ricou B: Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med* 161:121–123, 2001.