



Fever control using external cooling in septic shock: a randomized controlled trial



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Fever Control Using External Cooling in Septic Shock: A Randomized Controlled Trial

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FS, LBr, FL, and CB-B contributed to the study concept, design, and grant finding. FS, LBr, and SK, had access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. FS, KC, JDe, AM, ND, JDa, LBo, OB, and FC contributed to data collection. FS, LBr, and SK drafted the manuscript which was revised for important intellectual content by KC, JDe, AM, ND, JDa, LBo, OB, FC, FL, and CB-B.

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AT A GLANCE COMMENTARY

What is the current scientific knowledge on the subject: The benefits and risks of fever control in severe sepsis remain debated. Although fever is common in sepsis, few comparative studies on fever management are available.

What does this study adds to the field: Fever control using external cooling in sedated patients with septic shock is safe and decreases vasopressor requirement and early mortality.

This article has an online data supplement which is accessible from this issue's table of content on line at www.atsjournals.org

Abstract

Rationale: Fever control may improve vascular tone and decrease oxygen consumption, but fever may contribute to combat infection.

Objective: To determine whether fever control by external cooling diminishes vasopressor requirements in septic shock.

Methods: In a multicenter randomized controlled trial, febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation were allocated to external cooling (n=101) to achieve normothermia (36.5-37°C) for 48 hours or no external cooling (n=99). Vasopressors were tapered to maintain the same blood pressure target in the two groups. The primary endpoint was the number of patients with a 50% decrease in baseline vasopressor dose after 48 hours.

Measurements and main results: Body temperature was significantly lower in the cooling group after 2 hours of treatment (36.8 ± 0.7 vs. $38.4 \pm 1.1^\circ\text{C}$, $P < 0.01$). A 50% vasopressor dose decrease was significantly more common with external cooling from 12 hours of treatment (54% vs. 20%; absolute difference, 34%; 95% confidence interval [95%CI], -46 to -21; $P < 0.001$) but not at 48 hours (72% vs. 61%; absolute difference, 11%; 95%CI, -23 to 2). Shock reversal during the ICU stay was significantly more common with cooling (86% vs. 73%; absolute difference, 13%; 95%CI, 2 to 25; $P = 0.021$). Day-14 mortality was significantly lower in the cooling group (19% vs. 34%; absolute difference, -16%; 95%CI, -28 to -4; $P = 0.013$).

Conclusion: In this study, fever control using external cooling was safe and decreased vasopressor requirements and early mortality in septic shock.

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INTRODUCTION

“Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever...”

Sir William Osler (1)

Sepsis is a common syndrome responsible for multiorgan failure requiring intensive care unit (ICU) admission. Septic shock, defined as sepsis with cardiovascular failure requiring vasopressor infusion, has an extremely high mortality rate of 40%-60% (2, 3). The chances of survival are largely dependent on the course of the cardiovascular dysfunction (4). Current recommendations focus on the first few hours of sepsis management and include an early diagnosis, control of the infection source, and prompt restoration of tissue oxygenation (5). The criteria for vasopressor selection remain debated (6, 7). Low-dose corticosteroids have been suggested to enhance the resolution of cardiovascular dysfunction (5, 8, 9).

Among patients with severe sepsis, two-thirds have a fever, classically defined as a core body temperature above 38.3° C (10, 11). Fever occurs after tissue injury or infection, leading to leukocyte activation and release of pyrogenic cytokines (12). Although fever control is widely used in febrile ICU patients, its benefits and risks during sepsis have received little research attention (13-15). In severe sepsis, external cooling decreases the time to fever control without exposing the patient to the potential adverse effects of antipyretic drugs (16). Short-term physiological effects of fever control include decreases in cardiac output and oxygen consumption and increases in vascular tone and serum lactate clearance (16-19). However, fever may strengthen host defenses and increase survival (20, 21) and can inhibit the growth of microorganisms (22, 23).

To determine whether fever control by external cooling benefited ICU patients with early septic shock, we conducted a multicenter randomized controlled trial (“Sepsiscool”). Our primary endpoint was the proportion of patients with a 50% decrease in vasopressor requirements after 48 hours.

Part of the study results have been reported previously in abstract form (24).

METHODS

Patients

Adults with septic shock admitted to the seven participating ICUs between February 2008 and October 2009 were eligible. Inclusion criteria were documented or suspected infection (10) with a core body temperature $>38.3^{\circ}\text{C}$ and concomitant need for vasopressor infusion (epinephrine and/or norepinephrine), endotracheal mechanical ventilation, and intravenous sedation. The study protocol was approved by the appropriate ethics committee (*Comité de Protection des Personnes Ile-de-France IX, Créteil, France*). By French law, written informed consent was not required, as the standard of care encompasses both the study intervention and its absence (25). Patients or surrogates were informed about the trial and their right to refuse participation. Additional details on inclusion/exclusion criteria and the consent process are provided in an online data supplement (ODS).

Procedures

Centralized randomization was used to assign patients in a 1:1 ratio to external cooling or no external cooling. External cooling was used for 48 hours to maintain core body temperature between 36.5°C and 37°C . The mean arterial pressure (MAP) target was 65 mmHg or more in both groups (5). Weaning off vasopressors was managed by the nurses

according to an algorithm (Figure 1). Additional details on procedures are provided in the ODS.

Data collection and definitions

Severity of septic shock at inclusion was assessed using the SAPS 3 score (26) and SOFA score (27). Adjunctive treatments for septic shock were also recorded at inclusion and during the 48 hours of the study intervention. At baseline and during follow-up, we also recorded core body temperature, vital signs, vasopressor dose, SOFA score, and serum lactate concentration. Shock reversal was defined as absence, for the first time, of a need for vasopressors for 24 consecutive hours. Safety was assessed by recording episodes of hypothermia (temperature $\leq 34^{\circ}\text{C}$), shivering, seizures, and new episodes of nosocomial infections, until day 14. Additional details on data collection are provided in the ODS.

Endpoints

The primary endpoint was the number of patients with a 50% decrease in the baseline vasopressor dose after 48 hours. Secondary end points were the numbers of patients with a 50% baseline vasopressor dose decrease after 2, 12, 24, and 36 hours; the percentage of patients requiring a vasopressor dose increase within 48 hours after baseline; the percentage of patients with shock reversal in the ICU; the delta SOFA score vs. baseline; and all-cause mortality on day 14, at ICU discharge, and at hospital discharge.

Sample size and statistical analysis

Based on an observational pilot study (28), our hypothesis was that the proportion of patients achieving a 50% vasopressor dose decrease after 48 hours would increase from 50%

without cooling to 75% with cooling. To obtain 90% power with a two-sided alpha of 0.05, 85 patients were needed in each group.

All analyses were conducted on an intention-to-treat basis. Categorical variables were compared using the Chi² or Fisher exact test as appropriate. Continuous variables were compared using the Student t test or the Wilcoxon test in case of non-normal distribution. Bonferroni's correction was applied for the five pairwise comparisons of the proportions of patients with a 50% vasopressor dose decrease and for the comparisons of temperature and of MAP. Therefore, *P* values <0.01 were considered significant. Survival to day 14 was assessed using a Kaplan-Meier curve and log-rank test analysis. The incidence of nosocomial infections was compared using Poisson regression. *Post hoc* analyses adjusted on the baseline vasopressor dose, which differed significantly between groups, were performed for the comparisons of vasopressor requirements and mortality. Logistic regression was used to adjust the comparisons on dichotomous outcomes. We also performed analysis of covariance (ANCOVA) to assess the effect of cooling on the time-course of vasopressor requirements while taking into account the baseline vasopressor dose. Last, we investigated the robustness of our results on mortality in a sensitivity analysis excluding patients receiving baseline vasopressor doses above the 95th percentile. The method used for adjustment is detailed in the ODS. All analyses were performed using R 2.12.2 software (www.R-project.org).

RESULTS

Of the 579 screened patients, 200 were randomized, 101 to the cooling group and 99 to the no-cooling group (Figure 2). The most common reason for non-inclusion was absence of a fever (n=190, 32.8%).

In the cooling group, 3 patients did not receive cooling and 2 had cooling discontinued because of shivering. In the no-cooling group, 7 received cooling because of high temperature. All patients were kept in their randomization group for the analysis.

Patients in both groups were severely ill, as indicated by the high SAPS 3 and SOFA scores (Table 1). Infection characteristics were similar (Table 2). Most patients were admitted for medical reasons, of which the most common was pneumonia (70%). The two groups differed regarding vasopressor use at randomization, with significantly more patients receiving epinephrine in the no-cooling group ($P=0.004$) and norepinephrine in the cooling group ($P=0.023$). Both vasopressors were used in 5 patients in the no-cooling group and 1 patient in the cooling group (Table 1). The dose of each vasopressor was not significantly different between the two groups. The cumulated dose of both vasopressors, however, was slightly but significantly higher in the no-cooling group ($P=0.03$) (Table 1).

Core body temperature differed significantly throughout the 48-hour study period (Figure 3). The difference was largest after 12 hours. No patient received external cooling after 48 hours, and no rebound effect was observed within 24 hours after cooling discontinuation. The time-course of MAP was similar in the two groups, indicating similar and appropriate application of the algorithm for weaning off vasopressors (Figure 3). During the 48-hours study period, the initiation of new agents for shock stabilization was similar in the two groups (Table 3).

The percentage of patients with a 50% vasopressor dose decrease vs. baseline was significantly higher in the cooling group from 12 hours of treatment (absolute difference, 34%; 95% confidence interval [95%CI], 21% to 46%; $P<0.001$). The difference was not significant at 48 hours (Figure 4). After adjustment on the baseline vasopressor dose and on severity scores, these differences remained similar (Table 5). Using analysis of covariance to take into account the baseline vasopressor dose, we also found similar results. These

analyses also indicated that the significant effect of cooling was more pronounced in those patients having the highest baseline vasopressor doses (see ODS for details). Significantly fewer patients needed a vasopressor dose increase during the 48-hour study period in the cooling group (absolute difference, -18%; 95%CI, -4% to -31%).

Shock reversal was significantly more common in the cooling group (absolute difference, 13%; 95%CI, 2% to 25%) (Table 4). All these comparisons remained significant after adjustment on the baseline vasopressor-dose imbalance and severity (Table 5).

The delta SOFA score was significantly smaller in the cooling group (Table 4). Baseline renal function as assessed by the serum creatinine level and renal SOFA score was similar in the two groups (Table 1), but a larger proportion of patients required early renal replacement therapy in the no-cooling than in the cooling group (Table 4).

Survival to day 14 as estimated by the Kaplan-Meier curve was higher in the cooling group (Figure 5, log-rank $P=0.01$). The risk of death on day 14 was significantly lower in the cooling group and remained significantly different after adjustment on the baseline vasopressor-dose imbalance and on severity (odds ratio [OR], 0.36; 95%CI, 0.16-0.76) (Table 5). The sensitivity analysis excluding patients with very high baseline vasopressor doses did not modify the beneficial effect of cooling on survival (OR, 0.40; 95%CI, 0.18-0.87; $P=0.021$). The difference in mortality was no longer significant at ICU or hospital discharge (Table 5).

Neuromuscular blockers were already being used at baseline in 51 patients and were given to 32 additional patients during the 48-hour study-treatment period. The need for paralysis and sedation was similar in the two groups at baseline and during the 48-hour study treatment (Tables 1 and 3). Core body temperature, vasopressor requirements, and mortality were similar in patients who did and did not receive neuromuscular blockers (data not shown). No patient developed hypothermia. Seizures occurred in 4/99 patients in the no-

cooling group and 1/101 patients in the cooling group. The density of acquired infections by day 14 was 32.6/1000 ICU days (95%CI, 32.3-32.9) in the cooling group and 23.8/1000 ICU days (95%CI, 23.4-24.1) in the no-cooling group (OR, 1.37; 95%CI, 0.80-2.36), $P=0.25$.

DISCUSSION

In our study, external cooling to achieve normothermia in patients with septic shock was safe, accelerated hemodynamic stabilization, decreased vasopressor requirements, increased the rate of shock reversal, and decreased early mortality.

The dread of fever described by Sir William Osler a century ago remains valid (1). Several recent surveys showed that fever control was widely used in hospitals, usually at the initiative of the nurses (13, 14). Although fever is a very common symptom of infection, the indications for antipyretic treatments remain unclear. The controversy about fever control re-emerged in 2009 during the A/H1N1v influenza pandemic (22, 29, 30). Inhibition of virus replication by high temperatures has long been used as an argument against fever control during infectious diseases (31). Fever can exert a negative feedback on the release of pyrogenic cytokines, thereby modulating the inflammatory process (12). Harmful effects of fever control on host defenses and recovery from infection have been reported in experimental models of sepsis (20, 21). The increased risk of early infection acquisition after mild therapeutic hypothermia during surgery or after cardiac arrest is also seen as supporting a negative impact of fever control on host defenses (32, 33). It is important to stress that our goal was to control the fever and not to induce hypothermia. Also, all antipyretic drugs have side effects and may impair immune functions and recovery from infection (29, 34-36). A small randomized trial in trauma patients found higher incidences of infection and death when the temperature threshold for acetaminophen therapy was 38.5°C instead of 40°C (37).

In ICU patients, external cooling results in a rapid oxygen consumption decrease that may help to restore tissue oxygenation during shock (16, 19). During renal replacement therapy, thermal balance control significantly increases vascular tone and arterial pressure in septic patients (38, 39). The main limitations to the use of physical antipyretic methods are patient discomfort and the counterproductive effect of potential shivering (40). Suppression of shivering requires the use of sedating and paralyzing agents. In our study, external cooling was used in severely ill patients who were already receiving mechanical ventilation and sedation. The use of sedatives and neuromuscular blockers was not higher in cooled patients, and shivering occurred in only 2 patients. Because acute respiratory distress syndrome was common in our population, a large proportion of patients received neuromuscular blockers (83/200, 42%). The duration of cooling was kept short to allow monitoring of fever as a means of assessing the course of the initial infection and ensuring the early detection of nosocomial infection.

Our results show that fever control by external cooling is safe in the short-term of sepsis. Although we did not assess changes in immune function in our patients, recovery from the severe infection was not impaired in the cooling group. Our results are in agreement with a previous trial comparing ibuprofen to placebo in a large population of septic shock patients (17), in which mortality was not increased in the ibuprofen group, despite a rapid decrease in temperature. This study was not, however, designed to assess fever control. The impact of fever control may depend on the source of infection. In the ibuprofen study and our study, the main source of infection was the lung, whereas the available experimental data indicating a deleterious effect of fever control were obtained in peritonitis models (20, 21). In models of non-infectious lung inflammation, fever control was beneficial (41-44). Moreover, our results cannot be extrapolated to viral infections. In our study, most of the patients who received cooling were receiving appropriate antimicrobial therapy. The

possible negative impact of fever control on host defenses may be more pronounced when the source of infection remains uncontrolled.

Several hypotheses may explain the favorable impact of cooling in septic shock. Although we did not measure oxygen consumption, a decrease in oxygen consumption may be among main explanations for the faster hemodynamic stabilization and improved early survival. The more favorable course of organ failures suggests that tissue oxygenation was improved in the cooling group. Decreased exposure to vasopressors may also decrease the risk of adverse effects. All vasopressors can have unwanted effects on regional blood flow, heart rhythm, cardiac output, and acid-base balance (6, 7, 45). Although we did not specifically record these adverse effects, one hypothesis is that the beneficial effect of cooling was mediated by the vasopressor-sparing effect. The rapid effect of cooling in decreasing vasopressor requirements also raises the question of the mechanism by which other treatments help to reverse septic shock. Thus, the favorable hemodynamic effects of corticosteroids and continuous hemofiltration in septic patients may be related, at least in part, to the associated body temperature decrease (8, 9, 46).

The impact of cooling on shock reversal and early mortality in our patients is encouraging but must be interpreted in the light of the limitations of our study. The beneficial effect of cooling might be explained by a lower illness severity in this group, as reflected by the lower baseline dose of vasopressors. However, all other variables and scores strongly associated with outcomes in sepsis were well balanced between the two groups. Neither logistic regression nor ANCOVA changed the results compared to the unadjusted analyses on primary and secondary endpoints, indicating that the two groups were reasonably comparable at baseline and that the beneficial effect of cooling was not solely due to the baseline imbalance. Also, the sensitivity analysis confirmed the robustness of our results regarding mortality.

Blinding of group assignment after randomization was not feasible. Before the study, equal numbers of participating centers did and did not use fever control routinely in septic patients, strongly suggesting equipoise between the two approaches. To minimize bias, weaning off vasopressors was based on an algorithm and managed by the nurses, who presumably had minimal bias concerning the impact of fever control on blood pressure. The time-course of MAP was identical in the two groups, indicating fair application of the algorithm.

We did not record life-supporting treatments given before inclusion during the early phase of sepsis. The similarly short time to inclusion in the two groups indicates that most patients were randomized early during septic shock management. At inclusion, all patients had already received fluids and vasopressors, and most were receiving appropriate antibiotics indicating that the three mainstays of septic shock treatment were administered early in the vast majority of patients. The similar baseline SAPS 3 score, SOFA score, and blood lactate level in the two groups does not suggest an imbalance in the initial pre-enrollment treatment.

Our primary endpoint was the proportion of patients with a 50% vasopressor dose decrease after 48 hours vs. baseline. The difference in this endpoint was not statistically significant. However, the proportion of patients with a 50% vasopressor dose decrease differed between the two groups at the time when the difference in core body temperatures was greatest, i.e., at 12 hours. Also, the proportion of patients with a 50% vasopressor dose decrease was higher than expected based on our observational pilot study (28). The algorithm for vasopressor weaning, which was not used in the pilot study, accelerated the vasopressor dose decrease in both groups. Last, since vasopressors were started before randomization, the assessment occurred later than during our observational pilot study, in which patients were assessed 48 hours after vasopressor initiation. An at least 50%

vasopressor dose decrease was arbitrarily chosen as a clinically relevant criterion for shock improvement. We decided *a priori* to use a relative dose reduction, given the wide variability and asymmetric distribution of vasopressor doses administered in our previous pilot study (28). Shock reversal was another marker of shock evolution and also showed a significant difference in favor of cooling.

Our study was not designed or powered to examine survival and, consequently, no definitive conclusion on mortality can be drawn. The small baseline differences regarding the type and dose of vasopressors may suggest greater severity in the control group. However, the OR of day-14 mortality was not modified by adjusting on the baseline vasopressor dose imbalance and on severity, indicating that the significant difference was related to the cooling effect. Cooling prevented early deaths, as illustrated by the rapid separation of the survival curves (Figure 5). The mortality reduction was, however, not significant at ICU or hospital discharge, a fact that might suggest delayed side effects of cooling. We found a nonsignificant trend toward a higher incidence of nosocomial infections on day 14 in the cooling group. We cannot rule out that an increase in infections after day 14 might explain the later mortality in the cooling group. Because our goal was to look for beneficial effects of cooling used for only 48 hours, we chose short-term (day 14) endpoints to increase the likelihood of detecting effects during or just after cooling with less confounding due to the delayed impact of co-morbidities, complications, and mortality.

In conclusion, our study shows that fever control using external cooling in sedated patients with septic shock is safe and decreases vasopressor requirements and early mortality. Further larger studies are needed to confirm the positive signal of fever control on mortality and to determine whether mild hypothermia provides additional benefits.

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Figure legends

Figure 1: Algorithm used by nurses to wean patients off vasopressors in both groups

MAP, mean arterial pressure

Figure 2: Study flow-chart

Figure 3: Changes in body temperature and mean arterial pressure (MAP) over the first 72 hours after inclusion,* $P < 0.01$ (significant after Bonferroni's correction)

Panel A: time-course of core body temperature; the hatched zone represents the target core body temperature in the cooling group.

Panel B: MAP changes over time

Figure 4: Percentage of patients with a 50% vasopressor dose decrease vs. baseline during the first 48 hours after inclusion

* P was significant (< 0.01) after Bonferroni's correction

Figure 5: Kaplan-Meier survival curve for mortality until day 14

Figure 1

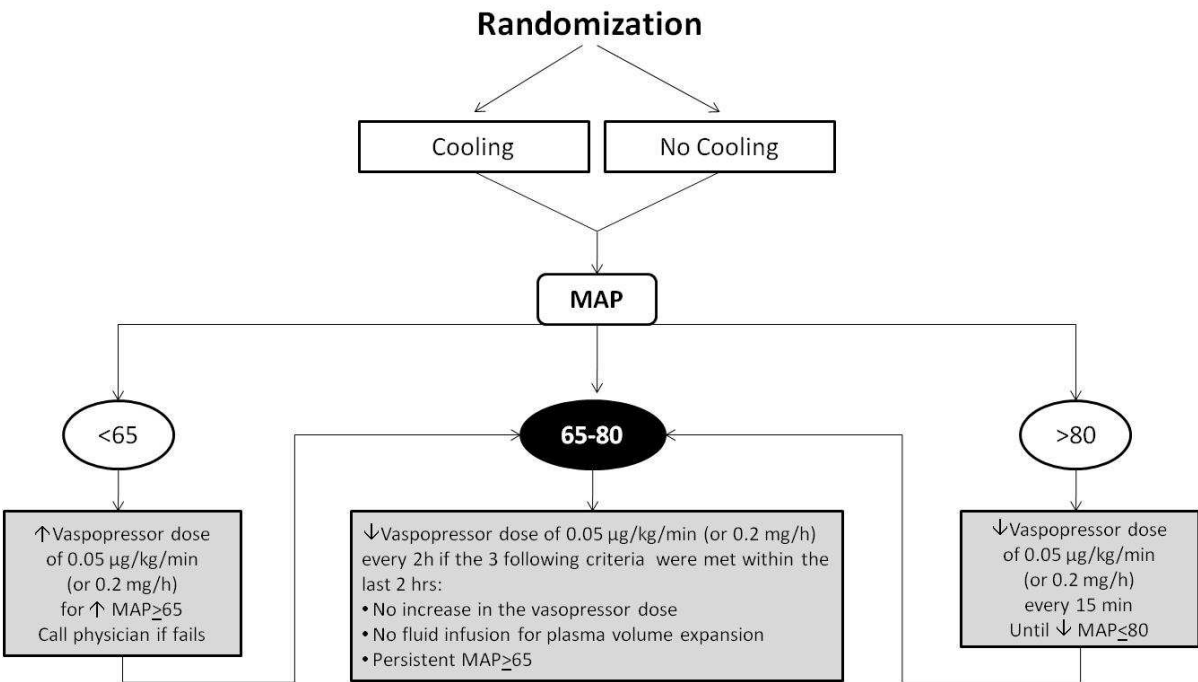


Figure 2

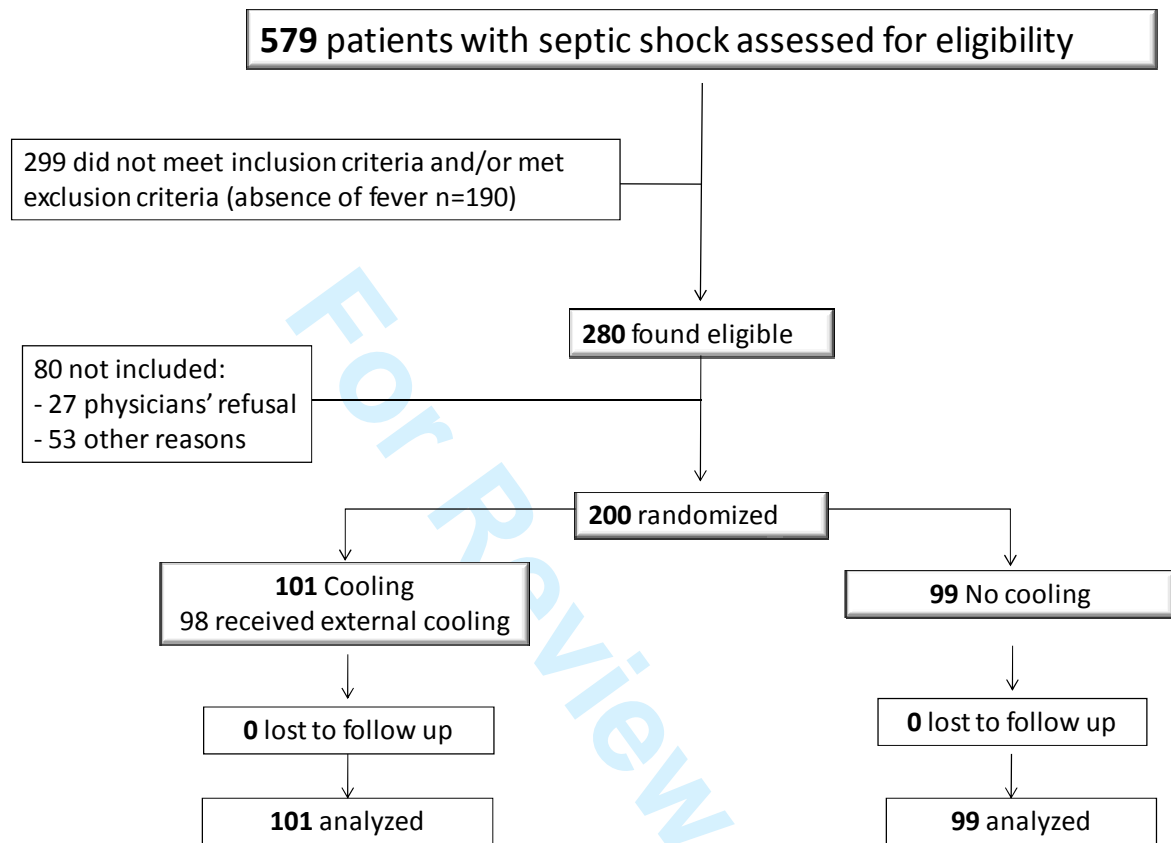


Figure 3

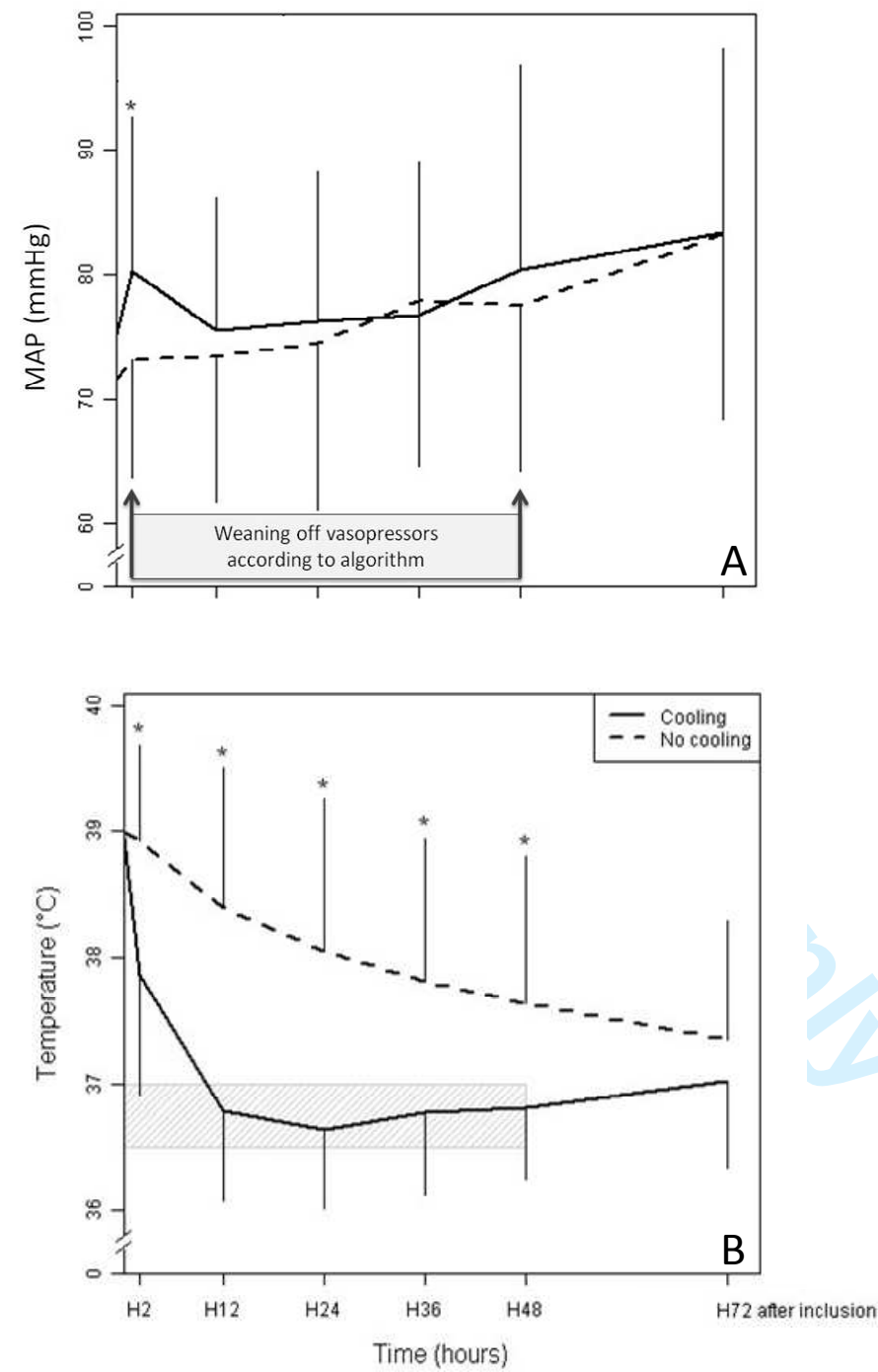


Figure 4

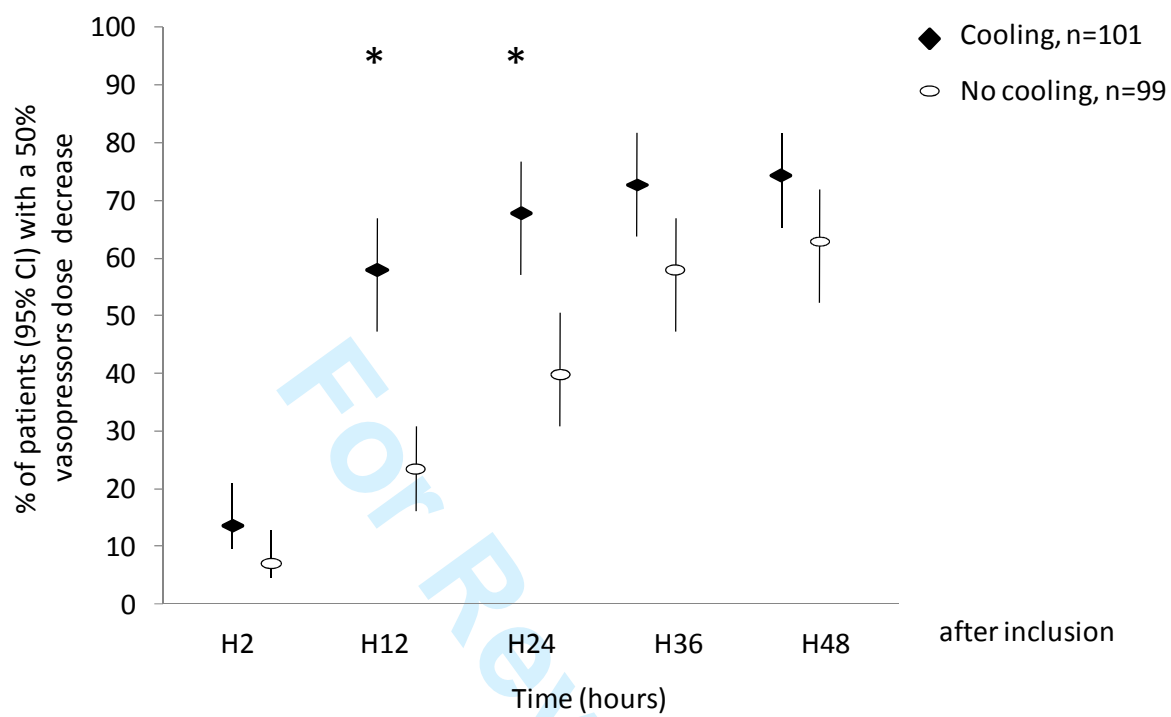


Figure 5

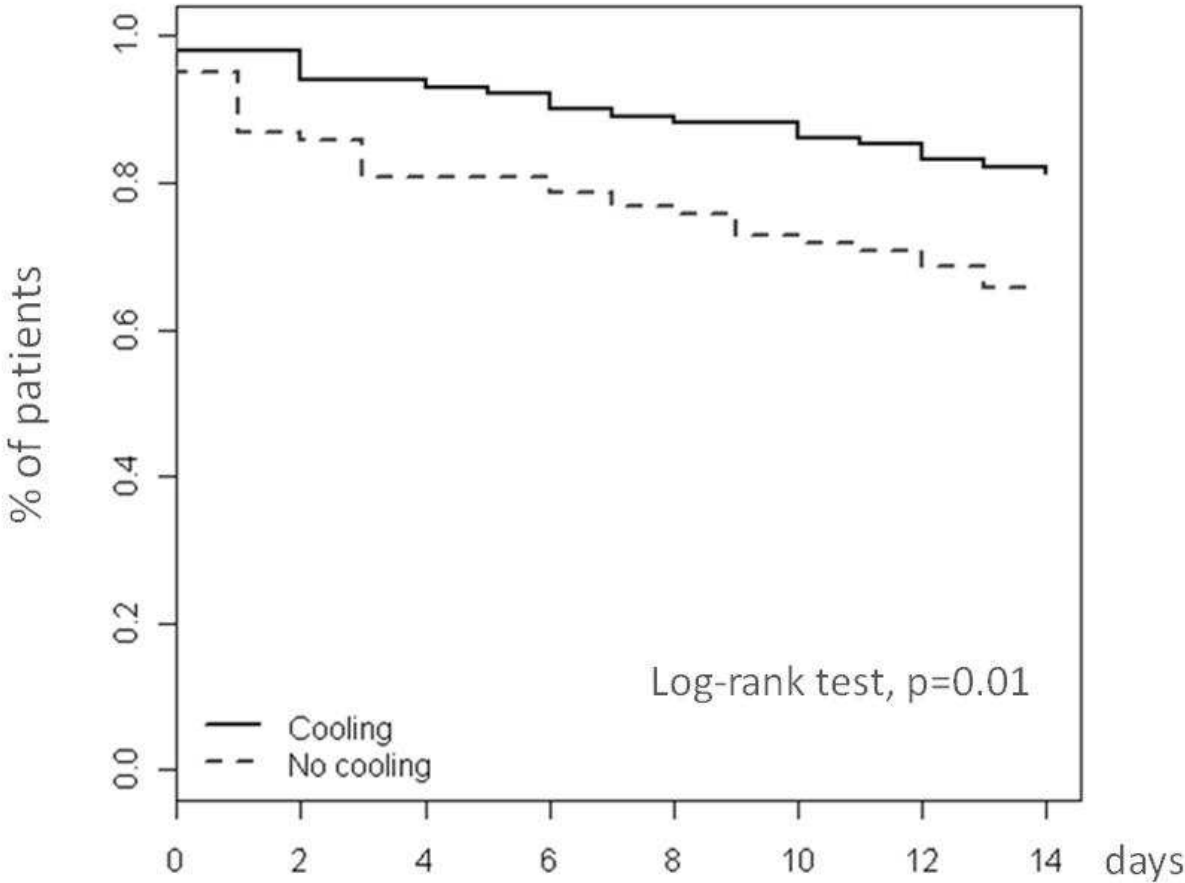


Table 1: Patient characteristics at baseline

	Cooling N=101	No Cooling N=99
Time from ICU admission to inclusion, d	1 (0-2)	1 (0-2)
Time from vasopressor initiation to inclusion, h	9 (3-19)	11 (4-21)
Location before ICU admission, n		
Emergency room	44	39
Medical ward	38	30
Surgical ward	7	15
Other ICU	12	15
Age, y	62 (51-70)	61 (49-70)
Males/Females, n	75/26	67/32
Weight, Kg	75 (67-86)	74 (61-88)
Fatal underlying disease [§] , n	42	43
Admission category, n		
Medical	84	82
Unplanned surgery	17	17
SAPS 3 score, points	77 (67-85)	79 (68-87)
Organ dysfunctions		
SOFA score, points	11 (9-14)	11 (9-14)
Number of organ failures [#]	2 (2-3)	2 (2-3)
Acute respiratory distress syndrome, n	54	45
PaO ₂ /FiO ₂ , mm Hg	165 (106-230)	153 (104-206)
Serum creatinine level, µmol/L	128 (82-208)	117 (76-222)
Renal failure, n [#]	22	26
Dialysis, n	8	8
Hemodynamic variables		
Mean arterial pressure, mm Hg	74 (69-80)	71 (65-78)
Serum lactate level, mmol/L	2.2 (1.4-3.4)	2.4 (1.3-3.5)
Vasopressor requirement		
Vasopressor infused at baseline, n		
Norepinephrine*	97	86
Epinephrine*	5	18
Epinephrine and norepinephrine	1	5
Vasopressor dose at baseline, µg/Kg/min		
Norepinephrine	0.50 (0.28-0.80)	0.65 (0.26-1.05)
Epinephrine	0.30 (0.21-0.33)	0.50 (0.27-0.66)
Epinephrine and norepinephrine*	0.50 (0.29-0.80)	0.63 (0.29-1.13)
Other treatments for sepsis, n		

Corticosteroids	46	39
Activated protein C	1	2
Vasopressin	4	4
Dobutamine	9	7
Neuromuscular blockers	24	27

Data are median (IQR) or number of patients.

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ-Failure Assessment; CNS, central nervous system

§ Underlying disease expected to cause death within 1 or 5 years according to the McCabe classification

#Defined as a SOFA score >2 points for each of the six organ functions assessed in the SOFA score

Defined as a renal SOFA score >2 points

* All variables were similar in the two groups except type and dose of vasopressor ($P<0.05$)

Table 2: Baseline characteristics of the infection

	Cooling N=101	No Cooling N=99
Temperature, °C	38.8 (38.6-39.2)	38.9 (38.5-39.3)
Type, n		
Community-acquired	53	43
Hospital-acquired	30	38
ICU-acquired	17	18
Source, n		
Lungs	71	67
Abdomen	5	8
Genitourinary tract	4	8
Other	15	13
Unknown	6	3
Pathogens recovered, n		
Gram-positive only	30	21
Gram-negative only	36	45
Mixed organisms	6	4
Other	6	2
No pathogen	23	27
Appropriate antimicrobial therapy, n		
Yes	83	84
No	13	11
Unknown	5	4

All variables were similar in the two groups.

Table 3: Other treatments given after inclusion and during the 48-hour study-treatment period

	Cooling n=101	No cooling n=99	<i>P</i> value
Treatments for hemodynamic stabilization			
Volume of fluids*, L	1.5 (0.5-2.0)	1.0 (0-2.5)	0.95
New treatment for shock			
Corticosteroids	17	21	0.69
Activated protein C	2	3	0.68
Vasopressin	1	1	>0.99
Dobutamine	6	7	>0.99
Other treatments			
Sedation, n	98	96	>0.99
Neuromuscular blockers, n	16	16	>0.99
Initiation of renal replacement therapy	10	21	0.030

* including fluids administered for shock reversal but not including fluids for nutrition and

for dehydration prevention

Table 4: Secondary outcomes

	Cooling n=101	No Cooling n=99	Between-group absolute difference (95% CI)	<i>P</i> value
Vasopressor requirement				
Patients requiring a vasopressor dose increase during the study- treatment period, n	35	52	-18 (-31 to -4)	0.011
Shock reversal in the ICU, n	87	72	13 (2 to 25)	0.021
Time-course of organ failures on D14				
SOFamax score, mean (SD)	11.4 (3.7)	12.3 (3.6)	-0.9 (-1.9 to 0.2)	0.10
Δ SOFA score, mean (SD)	0.2 (2.1)	1.1 (2.7)	-0.9 (-1.6 to -0.2)	0.010
Mortality rates				
D14, n	19	34	-16 (-28 to -4)	0.013
ICU discharge, n	35	43	-9 (-22 to 5)	0.20
Hospital discharge, n	43	48	- 6 (-19 to 8)	0.40
Length of stay				
In the ICU, d (mean [SD])	17(14)	16 (17)	1 (-3 to 5)	0.67
among ICU survivors	17 (14)	19 (16)	-2 (-6 to 2)	0.38
In the hospital, d (mean [SD])	36 (40)	28 (31)	9 (-1 to 19)	0.09
among hospital survivors	43 (39)	35 (26)	8 (-2 to 17)	0.56

Table 5: Adjusted outcomes

	Cooling n=101	No Cooling n=99	OR (95% CI), <i>P</i> value	Adjusted* OR (95% CI), <i>P</i> value
Vasopressor requirement				
N ^o of patients with a 50% vasopressor dose decrease at				
H2	11	4	2.90 (0.89-9.45)	3.74 (1.01-13.84)
H12	55	20	4.72 (2.52-8.85) [#]	5.07 (2.53-10.15) [#]
H24	66	37	3.03 (1.70-5.39) [#]	3.28 (1.72-6.28) [#]
H36	71	55	1.89 (1.06-3.39)	1.95 (1.05-3.65)
H48	73	61	1.62 (0.89-2.94)	1.65 (0.88-3.13)
Patients needing a vasopressor dose increase during study treatment, n	35	52	0.48 (0.27-0.85), 0.011	0.49 (0.27-0.90), 0.020
Shock reversal in the ICU, n	87	72	2.33 (1.14-4.77), 0.021	2.68 (1.17-6.16), 0.020
Mortality rates				
D14, n	19	34	0.44 (0.23-0.85), 0.013	0.36 (0.17-0.76), 0.008
ICU discharge, n	35	43	0.69 (0.39-1.22), 0.20	0.69 (0.35-1.33), 0.26
Hospital discharge, n	43	48	0.79 (0.45-1.38), 0.40	0.80 (0.42-1.53), 0.51

* Adjusted on the following baseline variables: vasopressor dose, SAPS 3 score, SOFA

score, McCabe classification, and appropriate antimicrobial therapy.

[#] *P*<0.01 (significant after Bonferroni's correction)

Online data supplement

Fever Control Using External Cooling in Septic Shock: A Randomized Controlled Trial

Frédérique Schortgen, Karine Clabault, Sandrine Katsahian, Jerome Devaquet, Alain Mercat, Nicolas Deye, Jean Dellamonica, Lila Bouadma, Fabrice Cook, Olfa Beji, Christian Brun-Buisson, François Lemaire, Laurent Brochard

Methods

Patients

Adults with septic shock admitted to the seven participating ICUs between February 2008 and October 2009 were eligible. Inclusion criteria were documented or suspected infection (i.e., gross pus at surgery, leukocytes in normally sterile fluid, abnormal focal opacity on the chest radiograph consistent with pneumonia, or purpura fulminans) (E1) with a core body temperature $>38.3^{\circ}\text{C}$, persistent hypotension despite fluid resuscitation requiring vasopressor infusion (epinephrine and/or norepinephrine) to maintain mean arterial pressure (MAP) ≥ 65 mmHg, endotracheal mechanical ventilation, and intravenous sedation. To be included, patients had to meet all five criteria concomitantly. There was no maximal time from meeting the five criteria to randomization. Documented or suspected infection could be present at ICU admission or acquired during the ICU stay.

Exclusion criteria were age <18 years, temperature $>41^{\circ}\text{C}$, pregnancy, continuous renal replacement therapy, administration of acetaminophen or nonsteroidal antiinflammatory drugs within 6 hours before inclusion, need for acetaminophen and/or nonsteroidal antiinflammatory drugs during the study-treatment period, burns, and Stevens-Johnson syndrome or toxic epidermal necrolysis.

A centralized interactive telephone system (Tech4Trials, Marly-le-Roi, France) was used to randomly assign patients in a 1:1 ratio to external cooling or no cooling. Patients were stratified by center with a random block size of six. Investigators were masked to block size. Blinding of group assignment after randomization was not feasible.

Consent process

The study protocol was approved for all centers (single advice) by the appropriate ethics committee (*Comité de Protection des Personnes Ile-de-France IX, Créteil, France*) and by the supervisory authority for data protection (*Commission Nationale Informatique et Libertés*). The ethics committee ruled that the study protocol complied with French law on clinical research with minimal risk to patients, i.e., research on the standard of care (*Recherche portant sur les soins courants*, L. 1121-1 of French Public Health Code, decree of March 9, 2007) (E2), which does not require written consent from participants but does require information on the study. In order to be allowed to use this specific provision, we ensured that the number of participating centers routinely using cooling in febrile sepsis was equal to those who did not. Accordingly, patients were to be informed about the trial and their right to refuse participation. The information process was specifically approved by the ethics committee. Because our patients with septic shock were not able to comprehend information, we conducted the formal oral and written information process before inclusion with a family member or other proxy, if present. Otherwise, proxies were informed as soon as possible when present in the unit. When possible, patients were informed about the trial and their right to refuse to continue to participate after septic shock recovery. In case of refusal, the law indicates that study follow-up and data collection must be stopped and the patient excluded, even if the family initially agreed to participation of the patient. No refusals occurred in our study.

Cooling procedure

In patients allocated to external cooling, either an automatic cooling blanket or ice-cold bed sheets and ice packs were used, according to usual practice at each center, with the objective of achieving normothermia (36.5°C to 37°C) within 2 hours after randomization. With automatic blankets, the target core body temperature was 36°C . Additional ice packs could be used if normothermia was not obtained within 2 hours. With ice-cold sheets and ice packs, the sheets were to be replaced when warmed by the body, i.e., every 30 minutes. Cooling was stopped if core body temperature fell below 36°C and restarted if core body temperature rose above 37°C . No cooling method was used during transport.

The use of neuromuscular blockers and sedatives was at the discretion of each participating center. In case of shivering, the physician in charge of the patient was free to choose between neuromuscular blockade or discontinuation of cooling. Management of sedation was not determined by the study protocol. Sedation was usually adjusted to patient needs by the nurses according to a written protocol in all participating centers. Midazolam and propofol were the most widely used sedatives.

External cooling was applied during 48 hours to maintain normothermia. No fever-control method was used in the no-cooling group; however, if core body temperature was above 41°C , the physician in charge of the patient could decide to start external cooling. In both groups, core body temperature was monitored continuously, using an esophageal, blood, or bladder probe, according to usual practice at each center. In both groups, fever control after the 48-hour study-treatment period was left at the discretion of the physician in charge of the patient.

Weaning off vasopressor therapy

In both groups, the target MAP was 65 mm Hg or more (E3). Vasopressors were used as continuous infusions with the dosage expressed as either mg/h or $\mu\text{g/Kg/min}$ according to standard practice in each center. For the analysis, all vasopressor doses were expressed as

$\mu\text{g/Kg/min}$. Weaning off vasopressor therapy could be initiated in patients meeting the following criteria for hemodynamic stabilization: no need to increase the vasopressor, no need for plasma volume expansion, and MAP remaining ≥ 65 mm Hg within the 2 hours after randomization. In both groups, vasopressor weaning was managed by the nurses according to an algorithm based on MAP values and using $0.05 \mu\text{g/Kg/min}$ (or 0.2 mg/h) dose decrements. The vasopressor infusion was stopped when the dose was $\leq 0.05 \mu\text{g/Kg/min}$ (or 0.2 mg/h) with MAP constantly ≥ 65 mm Hg for 2 hours.

Data collection and definitions

Patient characteristics and severity of septic shock recorded at randomization (baseline) included age, sex, weight, pre-existing co-morbidities assessed using the McCabe classification scheme (E4), admission category, SAPS 3 score (E5), presence and type of organ dysfunction using the sequential organ-failure assessment (SOFA) score (E6), and presence of acute respiratory distress syndrome (E7). Adjunctive treatments for septic shock were also recorded at baseline and during the 48-hour study-treatment period. Additionally, at baseline and during follow-up, we recorded core body temperature, vital signs, vasopressor dose, SOFA score, and serum lactate concentration. Shock reversal was defined as the first episode of vasopressor discontinuation for at least 24 hours. Safety of the study treatments was assessed by recording episodes of hypothermia (temperature $\leq 34^{\circ}\text{C}$); shivering; seizures; and new episodes of nosocomial infections, defined as infection occurring 48 hours or more after randomization.

Endpoints

The primary endpoint was the number of patients with a 50% decrease in the baseline vasopressor dose at the end of the 48-hour study-treatment period (H48). For patients receiving both epinephrine and norepinephrine, the baseline dose and H48 dose were calculated as the sum of the doses of each drug. In patients who died before H48, the

vasopressor dose at the time of death was recorded for computation of the percentage of change. Secondary endpoints were the numbers of patients with a 50% decrease in the baseline vasopressor dose at H2, H12, H24, and H36. Because of both the unexpected baseline imbalance and the significant difference in early mortality, some pre-specified endpoints would not bring any additional informations (i.e., vasopressor-free days on D14 and maximal vasopressor dose during the study-treatment period). We therefore compared the number of patients needing a vasopressor dose increase within 48 hours after randomization. We also recorded the percentage of patients with shock reversal in the ICU, the SOFA score change from baseline to the highest value after inclusion (E8), and all-cause mortality on day 14 and at ICU and at hospital discharge.

Sample size and statistical analysis

In a pilot study of septic shock, we found that half the patients achieved a 50% vasopressor dose decrease 48 hours after treatment initiation (E9). Our hypothesis was that external cooling would increase this proportion from 50% to 75%. To obtain 90% power with a two-sided alpha of 0.05, 85 patients were needed in each group. We decided to enroll 100 patients in each group to allow for patients being lost to follow-up or withdrawing consent.

All analyses were conducted on an intention-to-treat basis. Results are presented as the number of patients, median with the 25th – 75th interquartile range (IQR), or mean±SD. Because of the imbalance in the baseline vasopressor dose, *post hoc* logistic regression was performed to adjust for baseline covariates for dichotomous primary and secondary endpoints. We selected baseline variables previously found to have a significant impact on endpoints and without missing values. The number of selected covariates was determined by the sample size and number of missing data. The selected covariates were baseline vasopressor dose McCabe class, SAPS 3, SOFA, and appropriateness of antimicrobial

therapy. We then fitted a logistic model including these covariates and study-group assignment.

While our predefined primary endpoint was a dichotomous variable (number of patients with a 50% vasopressor dose decrease), we also compared the impact of cooling on the vasopressor dose decrease handled as a continuous variable. To this end, we performed analysis of covariance (ANCOVA) taking the baseline vasopressor dose into account. We found that the separate regression coefficients in each group were inhomogeneous at each posttreatment time point. Therefore, at each posttreatment time point, we tested the interaction between the baseline vasopressor dose and the group, to determine whether the coefficients were equal in the two groups (see Table A). The baseline vasopressor*group effect was significant at H2, H12, H24, indicating that the coefficients differed between the cooling and no-cooling groups. The significant between-group difference, i.e., the effect of cooling, was more pronounced in those patients having the highest baseline vasopressor doses.

Lastly, we investigated the robustness of our adjusted analysis on mortality in a sensitivity analysis excluding patients whose baseline vasopressor doses were above the 95th percentile of the population. All these excluded patients were in the no-cooling group.

Role of the funding source

The funding source did not participate in the study design, data collection, data analysis, data interpretation, or writing of the report. FS, SK, LB had full access to all the data and had final responsibility for the decision to submit for publication. All authors agreed to submit the final manuscript for publication.

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Table A: ANCOVA results for each posttreatment time point

		Estimate	95%CI	Pr(> t)
H2	(Intercept)	0.062	[-0.032;0.156]	0.194
	Cooling group	0.039	[-0.102;0.180]	0.587
	Baseline vasopressor dose	1.02	[0.951;1.088]	<0.001
	Cooling group* Baseline vasopressor dose	-0.209	[-0.365;-0.052]	0.01
H12	(Intercept)	-0.077	[-0.314;0.160]	0.525
	Cooling group	0.115	[-0.243;0.473]	0.529
	Baseline vasopressor dose	1.275	[1.101;1.449]	<0.001
	Cooling group* Baseline vasopressor dose	-0.577	[-0.970;-0.183]	0.005
H24	(Intercept)	-0.122	[-0.439;0.195]	0.455
	Cooling group	0.159	[-0.319;0.637]	0.514
	Baseline vasopressor dose	1.298	[1.061;1.535]	<0.001
	Cooling group* Baseline vasopressor dose	-0.705	[-1.236;-0.173]	0.01
H36	(Intercept)	0.06	[-0.189;0.309]	0.638
	Cooling group	0.05	[-0.320;0.420]	0.79
	Baseline vasopressor dose	0.616	[0.408;0.823]	<0.001
	Cooling group* Baseline vasopressor dose	-0.162	[-0.581;0.257]	0.452
H48	(Intercept)	-0.005	[-0.187;0.177]	0.955
	Cooling group	0.124	[-0.146;0.394]	0.369
	Baseline vasopressor dose	0.521	[0.370;0.671]	<0.001
	Cooling group* Baseline vasopressor dose	-0.202	[-0.507;0.103]	0.198