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

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***Rationale*: Fever control may improve vascular tone and decrease oxygen consumption, but fever may contribute to combat infection.**
***Objectives*: 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 ± 1.1°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 intensive care unit 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; $P = 0.013$).**
***Conclusions*: In this study, fever control using external cooling was safe and decreased vasopressor requirements and early mortality in septic shock.**

Keywords: septic shock; fever; intensive care unit; vasopressor agents

> 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)

AT A GLANCE COMMENTARY

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 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.

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).

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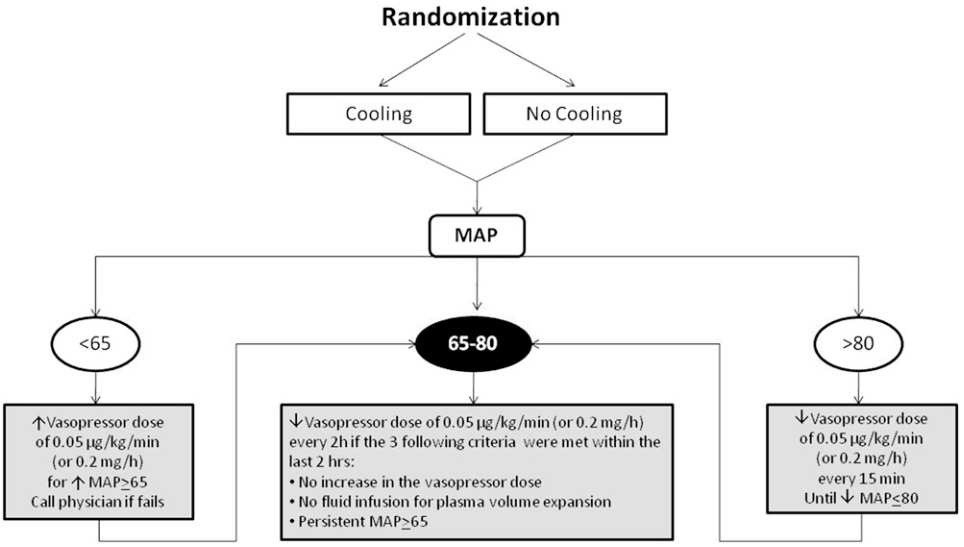

Figure 1. Algorithm used by nurses to wean patients off vasopressors in both groups. MAP = mean arterial pressure.

METHODS

Patients

Adults with septic shock admitted to the seven participating ICUs between February 2008 and October 2009 were eligible. Inclusion criteria consisted of documented or suspected infection (10) with a core body temperature greater than 38.3°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 the online supplement.

Procedures

Centralized randomization was used to assign patients at 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 mm Hg 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 online supplement.

Data Collection and Definitions

Severity of septic shock at inclusion was assessed on the basis of the Simplified Acute Physiology Score (SAPS) 3 score (26) and Sequential Organ Failure Assessment (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 the absence, for the first time, of a need for vasopressors for 24 consecutive hours. Safety was assessed by recording episodes of hypothermia (temperature $\leqslant$ 34°C), shivering, seizures, and new episodes of nosocomial infections, until Day 14. Additional details on data collection are provided in the online supplement.

Endpoints

The primary endpoint was the number of patients with a 50% decrease in the baseline vasopressor dose after 48 hours. Secondary endpoints were the numbers of patients with a 50% baseline vasopressor dose decrease after 2, 12, 24, and 36 hours; the percentage of patients requiring

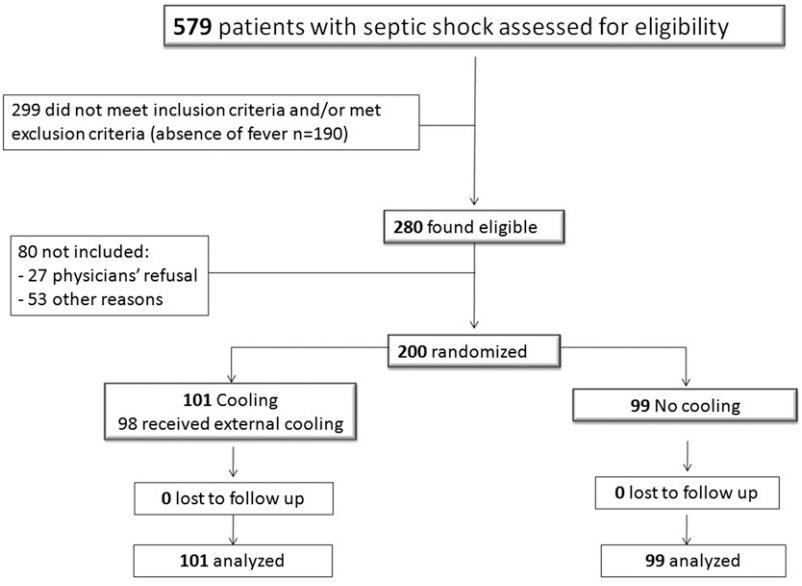

Figure 2. Study flowchart.

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, yr	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
Pa_{O_2}/FI_{O_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

Definition of abbreviations: FI_{O_2} = fraction of inspired oxygen; ICU = intensive care unit; IQR = interquartile range; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

Data represent median (IQR) or number of patients.

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

† Defined as a SOFA score greater than two points for each of the six organ functions assessed in the SOFA score.

‡ Defined as a renal SOFA score greater than two points.

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

a vasopressor dose increase within 48 hours of baseline; the percentage of patients with shock reversal in the ICU; the change in SOFA score (delta SOFA) versus baseline; and all-cause mortality on Day 14, at ICU discharge, and at hospital discharge.

Sample Size and Statistical Analysis

On the basis of 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 α of 0.05, 85 patients were needed in each group.

All analyses were conducted on an intention-to-treat basis. Categorical variables were compared by chi-square or Fisher exact test as appropriate. Continuous variables were compared by Student *t* test or Wilcoxon test in the case of nonnormal distribution. The Bonferroni correction was applied for the five pair-wise comparisons of the proportions of patients with a 50% vasopressor dose decrease and for the comparisons of temperature and of MAP. Therefore, *P* values less than 0.01 were considered significant. Survival to Day 14 was assessed with a Kaplan-Meier curve and log-rank test analysis. The incidence of nosocomial infections was compared by 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 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 online supplement. All analyses were performed with 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 noninclusion was absence of a fever (n = 190, 32.8%).

TABLE 2. BASELINE CHARACTERISTICS OF 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

Definition of abbreviation: ICU = intensive care unit.
All variables were similar in the two groups.

In the cooling group, three patients did not receive cooling and two had cooling discontinued because of shivering. In the no-cooling group, seven 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 five patients in the no-cooling group and in one 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 of 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-hour 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 versus 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 (*see* 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* the online supplement 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%).

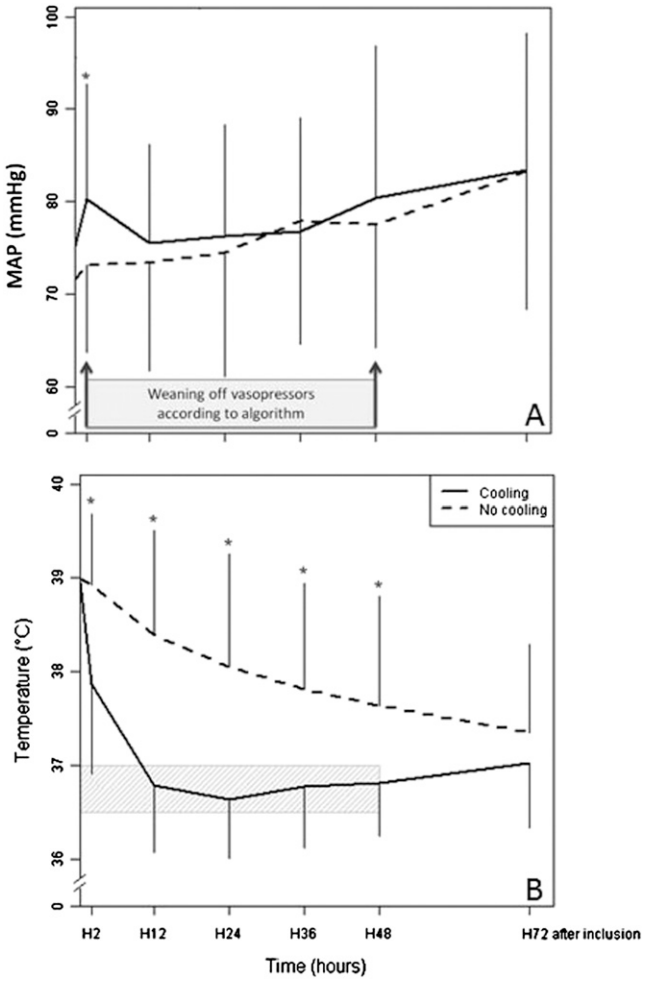

Figure 3. Changes in body temperature and mean arterial pressure (MAP) over the first 72 hours after inclusion; *$P < 0.01$ (significant after Bonferroni correction). (*A*) MAP changes over time. (*B*) Time course of core body temperature; the *hatched zone* represents the target core body temperature in the cooling group.

Shock reversal was significantly more common in the cooling group (absolute difference, 13%; 95% CI, 2 to 25%) (Table 4).

TABLE 3. OTHER TREATMENTS GIVEN AFTER INCLUSION AND DURING THE 48-HOUR STUDY-TREATMENT PERIOD

	Cooling (*n* = 101)	No Cooling (*n* = 99)	*P* 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.

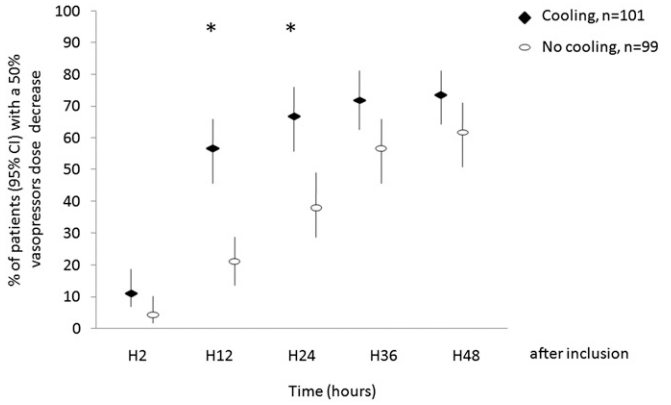

Figure 4. Percentage of patients with a 50% vasopressor dose decrease versus baseline during the first 48 hours after inclusion. *The *P* value was significant (<0.01) after Bonferroni correction. CI = confidence interval.

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 the 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 Kaplan-Meier curve analysis 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 of 99 patients in the no-cooling group and in 1 of 101 patients in the cooling group. The density of acquired infections by Day 14 was 32.6/1,000 ICU days (95% CI, 32.3–32.9) in the cooling group and 23.8/1,000 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 surveys showed that fever control was widely used in hospitals, usually at the initiative of the nurses (13, 14). Although fever is a common symptom of infection, the indications for antipyretic treatments remain unclear. The controversy about fever control reemerged in 2009 during the A/H1N1v influenza pandemic (22, 29, 30). Inhibition of viral 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

TABLE 4. SECONDARY OUTCOMES

	Cooling (*n = 101*)	No Cooling (*n = 99*)	Between-Group Absolute Difference (95% CI)	*P* 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 Day 14				
$SOFA_{max}$ score, mean (SD)	11.4 (3.7)	12.3 (3.6)	−0.9 (−1.9 to 0.2)	0.10
ΔSOFA score, mean (SD)	0.2 (2.1)	1.1 (2.7)	−0.9 (−1.6 to −0.2)	0.010
Mortality rates				
Day 14, 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

Definition of abbreviation: ICU = intensive care unit.

TABLE 5. ADJUSTED OUTCOMES

	Cooling ($n = 101$)	No Cooling ($n = 99$)	OR (95% CI); *P* Value	Adjusted* OR (95% CI); *P* Value
Vasopressor requirement				
No. of patients with a 50% vasopressor dose decrease at:				
Hour 2	11	4	2.90 (0.89–9.45)	3.74 (1.01–13.84)
Hour 12	55	20	4.72 (2.52–8.85)†	5.07 (2.53–10.15)†
Hour 24	66	37	3.03 (1.70–5.39)†	3.28 (1.72–6.28)†
Hour 36	71	55	1.89 (1.06–3.39)	1.95 (1.05–3.65)
Hour 48	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				
Day 14, 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

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; OR = odds ratio; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

* 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 correction).

and sedation. The use of sedatives and neuromuscular blockers was not higher in cooled patients, and shivering occurred in only two patients. Because acute respiratory distress syndrome was common in our population, a large proportion of patients received neuromuscular blockers (83 of 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 treatment 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 noninfectious 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 the 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 analysis of covariance changed the results compared with 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 due solely 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.

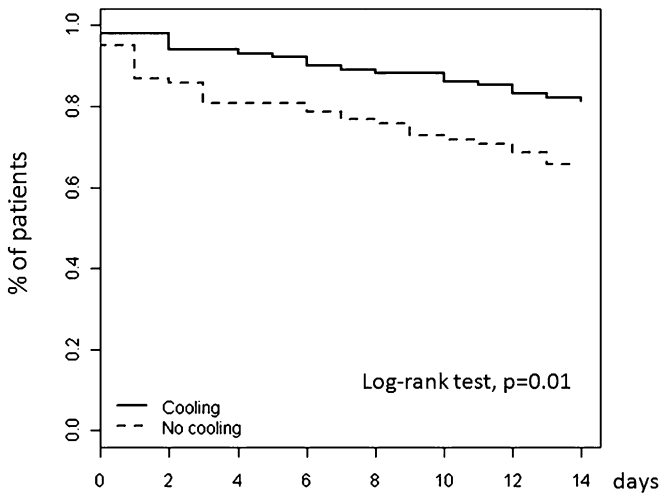

Figure 5. Kaplan-Meier survival curve for mortality until Day 14.

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 preenrollment treatment.

Our primary endpoint was the proportion of patients with a 50% vasopressor dose decrease after 48 hours versus 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, that is, 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, because 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 odds ratio 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 comorbidities, 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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