Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response

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Fonseca MT, Rodrigues AC, Cezar LC, Fujita A, Soriano FG, Steiner AA. Spontaneous hypothermia in human sepsis is a transient, self-limiting, and nonterminal response. J Appl Physiol 120: 1394–1401, 2016. First published March 17, 2016; doi:10.1152/japplphysiol.00004.2016.—Hypothermia in sepsis is generally perceived as something dysregulated and progressive although there has been no assessment on the natural course of this phenomenon in humans. This was the first study on the dynamics of hypothermia in septic patients not subjected to active rewarming, and the results were surprising. A sample of 50 subjects presenting with spontaneous hypothermia during sepsis was drawn from the 2005-2012 database of an academic hospital. Hypothermia was defined as body temperature below 36.0°C for longer than 2 h, with at least one reading of 35.5°C or less. The patients presented with 138 episodes of hypothermia, 21 at the time of the sepsis diagnosis and 117 with a later onset. However, hypothermia was uncommon in the final 12 h of life of the patients that succumbed. The majority (97.1%) of the hypothermic episodes were transient and self-limited; the median recovery time was 6 h; body temperature rarely fell below 34.0°C. Bidirectional oscillations in body temperature were evident in the course of hypothermia. Nearly half of the hypothermic episodes had onset in the absence of shock or respiratory distress, and the incidence of hypothermia was not increased during either of these conditions. Usage of antipyretic drugs, sedatives, neuroleptics, or other medications did not predict the onset of hypothermia. In conclusion, hypothermia was uncommon in the final 12 h of life of the patients that succumbed. The majority (97.1%) of the hypothermic episodes were transient and self-limited; the median recovery time was 6 h; body temperature rarely fell below 34.0°C. Bidirectional oscillations in body temperature were evident in the course of hypothermia. Nearly half of the hypothermic episodes had onset in the absence of shock or respiratory distress, and the incidence of hypothermia was not increased during either of these conditions. Usage of antipyretic drugs, sedatives, neuroleptics, or other medications did not predict the onset of hypothermia. In conclusion, hypothermia appears to be a predominantly transient, self-limiting, and nonterminal phenomenon that is inherent to human sepsis. These characteristics resemble those of the regulated hypothermia shown to replace fever in animal models of severe systemic inflammation.

When and how should caregivers interfere with the body temperature (Tb) of septic patients? This deceivingly simple question remains unanswered (23, 30, 42, 43), and the underlying problem is complicated by the fact that fever is not the only type of thermal manifestation in septic patients. Hypothermia occurs in 9–16% of the patients with sepsis (2, 6, 13, 21) and in 13–21% of the patients with septic shock (28, 34). Correlative studies have consistently demonstrated that the presence of hypothermia at the time of the sepsis diagnosis predicts poor outcome several days later (2, 6, 13, 21, 28, 34). This prognostic value of hypothermia, however, may simply reflect its higher prevalence in the most severe cases of sepsis (13, 21, 34), and it should not be taken as an indication that hypothermia itself worsens outcome (13). Despite that, hypothermia in sepsis is generally perceived as something dysregulated and accidental (8, 21), and prompt rewarming is regularly considered for those septic patients who display hypothermia (16). Such a conduct has been an impediment to understanding hypothermia in sepsis, to the extent that there is no published study on its dynamics and temporal associations with other components of the sepsis syndrome.

The clinical perception surrounding the role of hypothermia in sepsis contrasts with experimental studies in which the hypothermia induced by bacterial endotoxin in rats was shown to be a regulated, often transient thermoregulatory response that is brought about by downregulation of thermogenesis in conjunction with cold-seeking behavior (1, 39). Regulated hypothermia differs from accidental or forced hypothermia; the term regulated refers to a process in which an organism “wants” to become hypothermic and adjusts thermoeffector activity to achieve that goal, whereas the terms accidental and forced refer to a situation in which an organism is unable to maintain its Tb at the desired level, usually because of extreme cooling or thermoeffector failure. Some authors prefer the term anapyrexia to describe regulated forms of hypothermia, but, in practice, the terms anapyrexia and regulated hypothermia have been used interchangeably to refer to the same phenomenon (4, 5, 17, 18, 46). The regulated nature of hypothermia in endotoxemia has led to the hypothesis that a switch from fever to hypothermia may be an adaptive strategy to cope with the competitive demands that emerge in the face of an overt systemic inflammatory response (38, 40). More recently, direct experiments have shown that naturally occurring (spontaneous) hypothermia is more advantageous than fever in rats with severe forms of endotoxemia or Escherichia coli (E. coli)-induced sepsis (7, 26). Spontaneous hypothermia was even shown to be more advantageous than forced hypothermia in mice with severe endotoxemia (25).

It is clearly necessary to reconcile the evidence of regulated hypothermia in experimental models of systemic inflammation with the perception of hypothermia being a dysregulated phe-
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The present study took an important step in this direction by providing the first characterization of hypothermia in a cohort of septic patients not subjected to active rewarming. The dynamics of the response were described in terms of magnitude, duration, relationship to the stage of hospitalization, and, when applicable, relationship to the time of death. We also investigated whether there is any temporal relationship between the onset of hypothermia and the presence of septic shock or respiratory distress. Last, we investigated whether the onset of hypothermia was associated with the administration of antipyretics or other medications.

METHODS

With approval of the Institutional Review Board, data were extracted from the records of the adult intensive care unit (ICU) at the University of São Paulo Hospital (São Paulo, Brazil). Fifty consecutive patients meeting the inclusion criterion were sampled from a randomized database of patients diagnosed with sepsis according to the criteria of the Surviving Sepsis Campaign (9-11) over the period of March 2005 to August 2012. The inclusion criterion was the presence of hypothermia, either at the time sepsis was diagnosed or at a later stage of the ICU stay. Axillary thermometry was the standard method of \( T_b \) measurement; a fast-read digital thermometer with range of 32.0–42.9°C was used. According to the current guidelines, the \( T_b \) threshold for detection of hypothermia in sepsis is 36.0°C (11), without restrictions to specific thermometry methods. However, because axillary thermometry could underestimate core temperature by up to 0.5°C (3), we adopted a more conservative approach for detection of hypothermia, according to which values between 35.5°C and 36.0°C were considered hypothermic only when preceded, in the same episode, by at least one measurement of 35.5°C or less. Temporal correlation was also considered, where transient was defined as hypothermia followed by \( T_b \) reading of 36.0°C or higher. We investigated whether the presence of hypothermia was temporally associated with shock or respiratory distress. The presence of shock was inferred from mean arterial pressure \( \leq 60 \) mmHg, despite adequate fluid resuscitation, or from the use of vasopressors such as norepinephrine. The presence of respiratory distress was inferred from the use of positive-pressure mechanical ventilation through an endotracheal tube and, when available, from a ratio of \( < 300 \) for the partial pressure of arterial oxygen to the fraction of inspired oxygen. A bootstrap procedure was performed to estimate the 95% confidence intervals for the frequency of hypothermic episodes that developed in the absence or presence of shock or respiratory distress. The procedure was performed in two levels; a patient was drawn in the first level, and an episode of hypothermia from that patient was drawn in the second level.

We next investigated whether the onset of hypothermia was temporally associated with shock or respiratory distress. The time-lag cutoff was set at 12 h. A different analysis was employed for all other medications; such an analysis was less precise in the time domain and compared drug usage on the days of a hypothermic episode with drug usage on the adjacent, hypothermia-free days (previous and next). The 95% confidence intervals for drug usage were constructed by a bootstrap procedure for a two-level model, the first level being the patient and the second level being the days with relevant data from that patient. The statistical analyses were performed in the MATLAB software, with the exception of the three-dimensional correlation, which was done in Origin Pro 7.5.

RESULTS

Ninety-three patient records had to be reviewed to reach the target sample of 50 septic patients who developed hypothermia. Of these, six patients (6.5% of the records reviewed) displayed hypothermia exclusively at presentation (defined as the time sepsis was diagnosed), 15 patients (16.1%) displayed episodes of hypothermia at presentation and at later stages of the sepsis syndrome, and 29 patients (31.2%) were not hypothermic at presentation but became hypothermic at later stages. The median number of hypothermic episodes per patient was two, and the maximum number of episodes displayed by a single patient was 12. In Table 1, patients displaying a lower (\( \leq 2 \)) or a higher (\( > 3 \)) number of hypothermic episodes were classified according to the general characteristics of the cohort. The number of hypothermic episodes was not predicted by sex, race, age, source of infection, or the class of the infecting microorganism. Interestingly, although APACHE II scores and length of ICU stay did not predict the number of hypothermic episodes when considered independently (Table 1), the two of them together were correlated with the number of hypothermic episodes (Fig. 1). Mortality rate was 52%, and there was no evidence to conclude that there is a difference in mortality.
Table 1. Characteristics of septic patients who presented with one or more episodes of hypothermia

<table>
<thead>
<tr>
<th>Episodes of Hypothermia</th>
<th>≤ 2</th>
<th>≥ 3</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (42%)</td>
<td>11 (22%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>12 (24%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>23 (46%)</td>
<td>12 (24%)</td>
<td>0.102</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (20%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–45 yr</td>
<td>6 (12%)</td>
<td>4 (8%)</td>
<td>0.672</td>
</tr>
<tr>
<td>46–65 yr</td>
<td>11 (22%)</td>
<td>7 (14%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 yr</td>
<td>16 (32%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Source of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>9 (18%)</td>
<td>8 (16%)</td>
<td>0.355</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>9 (18%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (30%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>Infecting agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G- bacteria</td>
<td>12 (31%)</td>
<td>8 (21%)</td>
<td>0.540</td>
</tr>
<tr>
<td>G+ bacteria</td>
<td>6 (15%)</td>
<td>8 (21%)</td>
<td></td>
</tr>
<tr>
<td>Fungus</td>
<td>1 (2%)</td>
<td>4 (10%)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 19</td>
<td>20 (40%)</td>
<td>8 (16%)</td>
<td>0.239</td>
</tr>
<tr>
<td>&gt; 19</td>
<td>13 (26%)</td>
<td>9 (18%)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 days</td>
<td>13 (26%)</td>
<td>5 (10%)</td>
<td>0.269</td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>20 (40%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>Overall outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>17 (34%)</td>
<td>7 (14%)</td>
<td>0.693</td>
</tr>
<tr>
<td>Deceased</td>
<td>16 (32%)</td>
<td>10 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

G-, Gram negative; G+, Gram positive; APACHE, acute physiology and chronic health evaluation.

The stage of hospitalization was relevant for the development of hypothermia, with episodes of hypothermia being more concentrated in the initial 24 h of the ICU stay compared with the final 24 h (there was no overlap between the 95% confidence intervals; Fig. 3A). On the other hand, the period of the day was not a predictor for the onset of hypothermia; 52.1% of the episodes had onset at 00:00–11:59 vs. 47.9% with onset at 12:00–23:59. Shifting the time window by 6 h did not change the result; 57.3% of the episodes had onset at 06:00–17:59 vs. 42.7% with onset at 18:00–05:59. Perhaps most importantly, our study revealed that trends for reductions in Tb were as rare as the time of death approached (Fig. 3B). Over the 12-h period before death, trends for decreases in Tb were observed in only six patients, whereas trends for increases in Tb were observed in 18 patients (Fig. 3C). The median slope for the trends was significantly different from zero ($P = 0.022$). Besides, only two of the six terminal patients with negative trends reached a hypothermic level, as defined by values of 35.5°C or less (Fig. 3B).

In the next analysis, we sought for temporal relationships between the onset of hypothermia and the presence of circulatory shock or respiratory distress. The results demonstrated that nearly half of the hypothermic episodes began when patients were neither in shock nor in respiratory distress. Moreover, the chances of developing hypothermia were not increased in the presence of respiratory distress and, on the contrary, were reduced in the presence of shock (Fig. 4).

Finally, we evaluated whether hypothermia could be a pharmacotherapy-related event. Drugs with antipyretic activity were the first to be evaluated. Dipyrone was by far the most frequently used, having been administered in 97 of the 276 days included in this analysis. However, there was little or no overlap between the time of dipyrone administration and the time of the onset of hypothermia (Fig. 5); only 5.1% of the episodes had onset within the expected time frame for the administration of dipyrone.
the therapeutic effects of dipyrone, which averages 5 h in young adults (14) and can be prolonged by up to 75% in the elderly (49). Unfortunately, the same type of analysis could not be employed for the remainder of the drugs, as it was not viable to compile precise information regarding the time of their administration. As an alternative, the frequency of use of each drug in the days of hypothermia onset was compared with the frequency of use in adjacent, hypothermia-free days. Aside
from dipyrone, a total of 113 drugs were administered to the patients, which included sedatives, neuroleptics, anticonvulsants, and paralyzing agents, in addition to antimicrobials, anti-inflammatory drugs, analgesics, and cardiovascular-related drugs. For none of the drugs, regardless of class, did the frequency of use differ between hypothermia-containing and hypothermia-free days. In other words, the development of hypothermia was independent of drug usage. The results for the most frequently used drugs are presented in Table 2; for a complete list, see the supplemental data (supplemental material is available for this article online at the Journal of Applied Physiology website).

**DISCUSSION**

By evaluating the dynamics and other characteristics of hypothermia in septic patients not subjected to active rewarming, the present study revealed that hypothermia in human sepsis is a response that is predominantly transient, self-limiting, and nonterminal. In addition, bidirectional fluctuations in $T_b$ were evident during most of the responses. Taken together, these findings are compatible with the idea that septic patients with hypothermia retain the ability to defend $T_b$ from cooling but do so at a lower $T_b$ threshold. Another important finding of the present study is that there was no evidence of hypothermia being a byproduct from common physiological dysfunctions (such as shock or respiratory distress) or from pharmacological interventions.

Remarkably, the characteristics of the septic hypothermia reported herein for humans resemble those of hypothermia in rat endotoxemia, the model in which the thermoregulatory manifestations of systemic inflammation have been best characterized. In this model, hypothermia appears to be an inherent component of the systemic inflammatory response, prevailing over fever as systemic inflammation becomes more severe (37). The hypothermia occurs early, is usually transient, and does not seem to be a consequence of circulatory shock or respiratory dysfunction (7). The regulated nature of hypothermia in this model is underscored by studies showing that hypothermia is preceded by a downward shift in the $T_b$ threshold for activation of aerobic heat production (39) at a time when the capacity for aerobic metabolism is not compromised (7). This thermoeffector alteration is particularly effective for being coupled with cold-seeking behavior (1, 39). This early form of hypothermia can be followed by a progressive, terminal form of hypothermia when endotoxemia is lethal (39). The progressive form may even prevail over the transient form in other rodent species, such as the mouse (41, 48). However, based on the results of the present clinical assessment, it appears that the early, regulated form of hypothermia may be more relevant to human sepsis than the late, progressive form.

In previous clinical studies (2, 6, 13, 21, 28, 34), the prevalence of hypothermia in septic patients at the time of enrollment was reported to be 9–21%. A comparable number (22.6%) was obtained in the present study for the time of the sepsis diagnosis, but the present study also revealed a substantial number of patients (31.2% of the records reviewed) who did not display hypothermia at the time of diagnosis but became hypothermic at later stages. Therefore, hypothermia seems to be more common in sepsis than generally thought. Another point to consider is that it cannot be ruled out that the hypothermia observed at the time of diagnosis and the hypothermia that develops later in the course of sepsis might represent distinct phenomena. This possibility, nevertheless, loses force in the face of the similar dynamics for hypothermia at either of these stages.

Although the present study was not designed to evaluate how spontaneous hypothermia impacts outcome, some of the present findings should be discussed in relation to the previously reported association between hypothermia and poor outcome in sepsis. To begin with, Clemmer et al. (6) and Kushimoto et al. (21) reported a higher incidence of shock in patients who develop hypothermia, whereas the present study showed that hypothermia and shock rarely happen simultane-
compared with adjacent, hypothermia-free days.

Drug usage on days of hypothermia development

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Day With Hypothermia (Frequency of Use (95% Confidence Interval))</th>
<th>Hypothermia-Free Day (Frequency of Use (95% Confidence Interval))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedatives, neuroleptics, and anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam*</td>
<td>0.30 (0.20–0.42)</td>
<td>0.23 (0.12–0.36)</td>
</tr>
<tr>
<td>Phenytoin*</td>
<td>0.09 (0.01–0.24)</td>
<td>0.14 (0.01–0.31)</td>
</tr>
<tr>
<td>Diazepam*</td>
<td>0.09 (0.03–0.16)</td>
<td>0.12 (0.03–0.25)</td>
</tr>
<tr>
<td>Haloperidol*</td>
<td>0.07 (0.01–0.14)</td>
<td>0.08 (0.03–0.13)</td>
</tr>
<tr>
<td>Phenobarbital*</td>
<td>0.04 (0.00–0.13)</td>
<td>0.07 (0.00–0.20)</td>
</tr>
<tr>
<td>Paralyzing agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisatracurium besilate*</td>
<td>0.06 (0.01–0.12)</td>
<td>0.04 (0.00–0.11)</td>
</tr>
<tr>
<td>Pancuronium*</td>
<td>0.01 (0.00–0.04)</td>
<td>0.01 (0.00–0.02)</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.36 (0.24–0.48)</td>
<td>0.33 (0.22–0.45)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.20 (0.09–0.32)</td>
<td>0.30 (0.14–0.47)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.18 (0.08–0.31)</td>
<td>0.14 (0.05–0.25)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.17 (0.07–0.29)</td>
<td>0.17 (0.09–0.26)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.14 (0.06–0.26)</td>
<td>0.08 (0.03–0.14)</td>
</tr>
<tr>
<td>Anti-inflammatory drugs and analgesics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl*</td>
<td>0.34 (0.22–0.46)</td>
<td>0.29 (0.17–0.42)</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>0.30 (0.17–0.45)</td>
<td>0.28 (0.16–0.41)</td>
</tr>
<tr>
<td>Tramadol*</td>
<td>0.14 (0.05–0.29)</td>
<td>0.08 (0.00–0.21)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.10 (0.02–0.20)</td>
<td>0.12 (0.03–0.25)</td>
</tr>
<tr>
<td>Methadone*</td>
<td>0.07 (0.01–0.14)</td>
<td>0.10 (0.02–0.20)</td>
</tr>
<tr>
<td>Cardiovascular-related drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>0.59 (0.42–0.76)</td>
<td>0.70 (0.49–0.93)</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>0.22 (0.16–0.30)</td>
<td>0.28 (0.19–0.39)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0.21 (0.05–0.41)</td>
<td>0.22 (0.05–0.45)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.17 (0.08–0.30)</td>
<td>0.20 (0.08–0.36)</td>
</tr>
<tr>
<td>Hydralazine*</td>
<td>0.12 (0.01–0.28)</td>
<td>0.12 (0.01–0.31)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>0.61 (0.39–0.87)</td>
<td>0.68 (0.43–0.97)</td>
</tr>
<tr>
<td>Insulin*</td>
<td>0.41 (0.25–0.61)</td>
<td>0.46 (0.27–0.69)</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>0.22 (0.13–0.33)</td>
<td>0.22 (0.13–0.32)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>0.17 (0.11–0.25)</td>
<td>0.17 (0.10–0.25)</td>
</tr>
<tr>
<td>Alizapride</td>
<td>0.14 (0.04–0.28)</td>
<td>0.17 (0.05–0.32)</td>
</tr>
</tbody>
</table>

Only the most frequently used drugs are shown here. For a complete list, see the supplemental material online. Drugs with any potential to lower body temperature or to suppress cold defense are marked with an asterisk (*).

The case of shock, hypothermia may predict mortality for occurring more frequently in sicker patients. In our opinion, the debate surrounding the adaptive vs. maladaptive role of hypothermia in sepsis can only be settled by a prospective, interventional study in which the hypothermic subset of septic patients is randomized into two groups: one group subjected to rewarming as soon as hypothermia is detected (the standard of care in many hospitals) and the other group having hypothermia run its natural course (perhaps within certain limits). Interestingly, when a similar design was applied to rats with *E. coli*-induced septic shock, the outcome was more favorable in the group that was allowed to develop hypothermia (26).

As far as methodological issues are concerned, it should be pointed out that the sites of T_b measurement were not reported in many of the previous studies on septic hypothermia (2, 6, 13, 28), and, when reported (21, 34), they were not standardized, including measurements of axillary, rectal, arterial, and bladder temperatures. In the present study, axillary thermometry was the standard (and the only) method of T_b measurement available in the ICU records reviewed. While the use of a standard methodology is a strength, it should be recognized that axillary thermometry has the limitation of being less precise than other more invasive methods such as pulmonary artery, bladder, and esophageal thermometry; for a review, see Barnason et al. (3). This limitation, however, should not be seen as evidence that axillary temperature bears no value, particularly in view of the rare nature of the patient cohort investigated in the present study. The temperature offset between axillary and pulmonary-artery temperatures usually does not exceed 0.5°C, and, most importantly, the offset remains relatively constant over a wide T_b range, so that satisfactory agreement indices have been reported between axillary temperature and temperatures at deeper body sites (22, 24, 32). On the basis of this knowledge, we were able to adopt conservative measures to prevent the inadvertent inclusion of borderline subjects in the hypothermic group. More specifically, we chose to consider as hypothermic only those patients who displayed at least one T_b reading of 35.5°C or less, a value that is at least 0.5°C below the currently established threshold for the diagnostic of hypothermia in sepsis (11).

Another methodological point that deserves comment is that neither the present study nor the previous clinical studies on septic hypothermia included assessments of the ambient temperature, despite the fact that this is of great importance for the development of fever vs. hypothermia in rodent models of systemic inflammation and sepsis (37). Furthermore, an observational study performed during the European heat wave of 2003 showed that the T_b of infected critically ill patients is more sensitive to changes in the ambient temperature than the T_b of their uninfected counterparts (47). Such a dependency on the ambient temperature (poikilothermia) is often seen as evidence of thermoregulatory dysfunction (27), but it should be noted that this interpretation reflects an outdated thermoregulation model, according to which all thermoeffectors are supposedly tied together to a single, integrated T_b set point. This model has been recently revised in view of the realization that thermoeffectors function independently of each other and can defend different levels of T_b in a regulated thermoregulatory response (20, 29, 33, 35, 36). In the case of experimental systemic inflammation, doses of endotoxin that cause a downward shift in the T_b threshold for activation of thermogenesis...
were found to produce the opposite effect or little change in the $T_b$ threshold for activation of heat loss effectors (19, 39). As a consequence of this threshold dissociation, thermal preference becomes the primary determinant of the physiological $T_b$ response, with more severe forms of endotoxia being associated with cold-seeking behavior and hypothermia and less severe forms being associated with warmth-seeking behavior and fever, at least in rats (1). If similar mechanisms happen to be at work in humans, there will be a need to devise protocols to cope with the loss of behavioral thermoregulation in sedated patients.

In conclusion, the present study was the first to characterize the dynamics of spontaneous hypothermia in human sepsis. The results may be paradigm shifting for portraying hypothermia as a transient, self-limiting, and nonterminal response, as opposed to a dysregulated, progressive phenomenon. As discussed above, the dynamics of septic hypothermia reported herein resemble those of the regulated hypothermia described in animal models of systemic inflammation, in which hypothermia naturally replaces fever as systemic inflammation escalates in severity. This notion is in line with the provocative hypothesis put forward by Singer and colleagues (31, 44) to explain metabolic shutdown in sepsis on the bases of evolutionarily conserved, adaptive mechanisms. Surprisingly, though, the link between hypothermia and metabolic shutdown has not yet been demonstrated in human sepsis, despite the fact that these two phenomena are known to be deeply intertwined in experimental models (7, 12, 39, 45). Taken together, these observations raise the question as to whether rewarming is at all necessary in the subset of septic patients who naturally become hypothermic. Although this question can only be answered with prospective intervention, the present study provides essential background information for future trials.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.T.F. and L.C.C. collected data; M.T.F., A.C.R., A.F., F.G.S., and A.A.S. analyzed data; M.T.F., A.C.R., A.F., F.G.S., and A.A.S. interpreted results; M.T.F. and A.A.S. prepared figures; M.T.F. and A.A.S. drafted manuscript; M.T.F., A.F., F.G.S., and A.A.S. edited and revised manuscript; M.T.F., A.C.R., L.C.C., A.F., F.G.S., and A.A.S. approved final version of manuscript; F.G.S. and A.A.S. conception and design of research.

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