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Hypothermia and Sepsis

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1. ABSTRACT

Alterations in body temperature may be frequently observed in patients and experimental animals. Systemic infections may alter the host body temperature, and a pre-existing altered body temperature may modulate the host response to infection. Septic patients who develop hypothermia have a significantly worse outcome than those who develop a fever or maintain a normal body temperature. Perioperative hypothermia may occur as a result from anesthetic action, surgical procedures, or specific targeted interventions. This perioperative hypothermia is associated with adverse outcomes including increased surgical wound infections. In animal models of sepsis, perioperative hypothermia is also associated with a worse outcome and specific alterations of the inflammatory response. Understanding the mechanisms of why the host response to infection is impaired by pre-existing hypothermia will both improve our basic understanding of disease as well as identify potential targets for modulation.

2. INTRODUCTION

Alterations in body temperature may have a significant impact on the mortality of experimental animals with sepsis or patients with sepsis. The alterations in body temperature may be divided into two groups based on the chronology of when the temperature changes relative to the infectious disease process. The first group would be composed of patients or animals who have temperature changes that become manifest as sepsis evolves. In this group, the experimental animal or the patient is normothermic and the infectious disease process causes a change in the body temperature. The altered temperature may be either hypothermia or hyperthermia. This will be discussed and data provided indicating that hypothermia is a significant risk factor for a poor outcome in sepsis. However, this is not the focus of the present communication.

The second group consists of patients or animals where hypothermia precedes the onset of the septic insult.

In this situation, the natural history of the septic process may be significantly altered by the pre-existing decreased body temperature. This hypothermia may be the result of anesthetic action, induced hypothermia to provide protection from ischemic events, or prolonged exposure to the cold.

This review will focus primarily on the impact of hypothermia on the alterations observed in septic patients and animals, rather than sepsis induced hypothermia. This is particularly timely, since perioperative hypothermia is known to be associated with adverse outcomes although it must be acknowledged that the entire concept of whether hyperthermia or hypothermia are injurious or beneficial is actively debated (1, 2). This article will review both the clinical data as well as some of the basic mechanisms of how initial hypothermia may result in a poor outcome in response to a septic challenge.

3. BODY TEMPERATURE RESPONSE TO INFECTION

Mammals differ in their response to infectious challenges. Humans will typically have an elevation in their body temperature which of course is known as a fever. There is also a subset of patients who develop a lower body temperature, and these will be discussed in greater detail below. Many sepsis experiments are performed with rodents, either rats or mice. In contrast to humans, most rodents typically have a decrease in their body temperature in response to a significant infection (3). This hypothermic response has been recognized for over 50 years (4, 5). In fact, one of the very first papers was published in 1939 showing that mice injected with a lethal dose of pneumococcal bacteria would decrease their body temperature (6).

Mice and rats develop hypothermia when given either a lethal injection of endotoxin (7-9) or have sepsis induced in an experimental model of peritonitis (10-12). Hypothermia has also been documented to occur after fungal infections in mice (13). Additionally, mice with peritonitis will show a rapid fall in body temperature following antibiotic treatment (11). This represents a fundamental difference in the response to infection between rodents and humans. It must be noted that mice will develop a rise in body temperature following injection of endotoxin but only under special circumstances. Specifically, mice need to be housed at a room temperature of 29°C prior to the injection of the endotoxin (14). In contrast, humans at room temperature will develop a fever following injection of endotoxin (15). Sheep are more similar to humans and develop fever after sepsis, and also similar to humans those exhibiting hypothermia have a greater mortality (16).

Given these differences in the response to either endotoxin or a bacterial challenge, it is not appropriate to compare the hypothermic response of a septic rodent to a septic human who has a hypothermic response. In the human the typical response is an increase in body temperature while in the rodent the typical response is a decrease. This fundamental difference is important to bear in mind when evaluating the basic science literature documenting the natural history of the septic response.

4. SEPSIS INDUCED HYPOTHERMIA IN PATIENTS PORTENDS A POOR PROGNOSIS

Previous authors have documented that patients with sepsis who develop hypothermia have a significantly worse prognosis compared to those with a fever or those who are normothermic. There can be difficulty in evaluating different clinical papers since there is limited consensus in defining the appropriate temperature for documenting the presence of hypothermia. In one study hypothermia was defined as a body temperature <35 .5°C (17). With this definition, 9% of septic patients from a large clinical trial had documented hypothermia. Mortality in this group was significantly higher, 62% versus 26% in those without hypothermia. Additionally, those patients with hypothermia progressed more rapidly to death. In another study, 10% of participants had hypothermia and this was also associated with significantly worse mortality (70% in the patients with decreased body temperature compared to 35% in febrile patients) (18). In addition to having greater mortality, there are other differences observed in patients with sepsis and hypothermia such as hemodynamic alterations (19). Yet another study showed a doubling of the mortality rate among patients with sepsis induced hypothermia (20). A very recent study published in the past year showed that hypothermia developed in approximately 9% of patients compared to fever which occurred in 28% of patients (21). Those patients with hypothermia had much higher sequential organ failure assessment scores. As in the other studies, the septic patients with hypothermia in this study had a much worse mortality. It has been emphasized that among the elderly hypothermia may be one of the initial signs of sepsis (22). After an extensive review of the published literature it appears that every published study shows a worse prognosis in septic patients who develop hypothermia. These previous papers are summarized in Table 1.

5. THE IMPACT OF PRE-EXISTING HYPOTHERMIA

5.1. Clinical Observations

Patients with marked hypothermia are at increased risk for the development of severe infections. Those individuals with prolonged exposure to the cold with resulting hypothermia frequently develop infections which may be occult since they fail to manifest typical signs of infection (23). However, many of these patients also suffered from chronic alcoholism with impaired cerebral function so the risk of infection may not be solely related to the hypothermia. The observed level of hypothermia in these patients was frequently extreme. For example some of these patients had core body temperatures below 22°C and survived. It would be difficult to extrapolate from the severe cases to routine clinical practice where depressed body temperature may be observed during surgery. A recent publication showed that among newborns, hypothermia on admission is a significant risk factor for any type of death (24).

Table 1. Human infectious diseases with hypothermia as a risk factor for increased mortality

Disease	# of Patients	Increased mortality	Year of publication (reference number)
Sepsis Syndrome	1333	Yes	1990 (43)
Patients hospitalized with shigellosis	9780	Yes	1990 (44)
Elderly patients with septicemia	175	Yes	1990 (45)
Bacteremia during diarrhea	1824	Yes	1991 (46)
Severe Sepsis and Septic Shock	11,828	Yes	1995 (47)
Bacteremic Sepsis	5457	Yes	1996 (48)
Neonatal Patients with Sepsis	171	Yes	1996 (49)
Sepsis	455	Yes	1999 (50)
Pneumonia patients with bacteremia	4548	Yes	2000 (51)
Septic Shock	930	Yes	2000 (52)
Bloodstream Associated Sepsis and Septic Shock	1981	Yes	2004 (53)
Invasive infection with Streptococcus pneumoniae	464	Yes	2004 (54)
Neonatal patients with sepsis identified by village health care workers	3567	Yes	2005 (55)
Neonatal patients with sepsis	763	Yes	2005 (56)

Peri-operative hypothermia may develop as a response to anesthetic actions since the typical response to many of the anesthetics is a rapid drop in body temperature. The causes of this hypothermia are multi-factorial, but the end result is that some patients demonstrate peri-operative hypothermia.

Perioperative hypothermia has several deleterious consequences. One of the most important is a significant increase in adverse cardiac events (25), although other problems may also arise (26-28). It is been reported that there is an increase in surgical wound infections associated with perioperative hypothermia. In a prospective randomized study patients with hypothermia developed wound infections at a rate of 19% while those with normal peri-operative temperature only had a 6% incidence of wound infection (29). These results were verified in subsequent studies which also documented that maintaining normothermia during surgery results in fewer wound infections (30, 31). An unresolved issue is whether systemic infections such as sepsis would also be reduced if perioperative hypothermia were prevented or corrected (28). Observations such as these have led to different efforts to identify optimal methods for warming patients in order to maintain perioperative normothermia (32). Additionally, animal studies have been initiated to determine whether systemic infections would result in a worse outcome if they occurred following perioperative hypothermia. These animal studies also attempted to provide some basic science insights into the mechanisms of why perioperative hypothermia exerts a deleterious outcome.

5.2. Animal studies documenting a worse outcome with systemic infections following perioperative hypothermia

There are two studies which have clearly demonstrated that perioperative hypothermia is associated with a worse outcome from a systemic infection. In one of these, anesthesia was induced with ketamine\xylazine which induces a prompt decrease in body temperature (33). The experimental model of sepsis resulting from peritonitis induced by cecal ligation and puncture was used for this study. One of the first aspects of this work was to document the temperature alterations that occur following exposure to anesthesia and differentiate the anesthesia hypothermia from the sepsis hypothermia. Ketamine\xylazine induces a rapid decrease in body temperature, within minutes following exposure as shown in Figure 1. We followed the decline in body temperature by implanting radio transmitters which closely follow the animals' temperature (34). This substantial drop in temperature with ketamine/xylazine was not observed in mice with isoflurane anesthesia. While a discussion of temperature alterations induced by different anesthetic actions is beyond the scope of this article, these data clearly demonstrate substantial differences in the core body temperatures induced by ketamine/xylazine compared to isoflurane.

We also examined the effects of peri-operative warming on the temperature response and designed an experiment to determine whether we could correct the anesthesia induced perioperative hypothermia by external warming (33). For the studies, mice were placed for one hour in a warmed cage kept at a constant temperature of 35°C. The warmed cage was generated by placing a cage, including the micro-isolator cage top and bedding, on top of a pad connected to a circulating water bath. Placing the mice in the warmed cage for one hour had a profound effect on the animal's body temperature. As can be observed in figure 1, this warming is able to substantially reverse the hypothermia. The one hour of warming was able to maintain the animal near the normal body temperature of 36.5° C. Warming also helped prevent the hypothermia observed with isoflurane anesthesia.

Ketamine/xylazine induces profound hypothermia such that the animal's body temperature drops below 30°C. As can be observed in figure 1, the animal slowly recovers from this hypothermia and by about 10 hours after the initial anesthetic the body temperature will have returned to normal. Despite the observed anesthesia induced hypothermia, none of these sham operated animals that merely had the radiotransmitter implanted died over the 14 day time interval of this study.

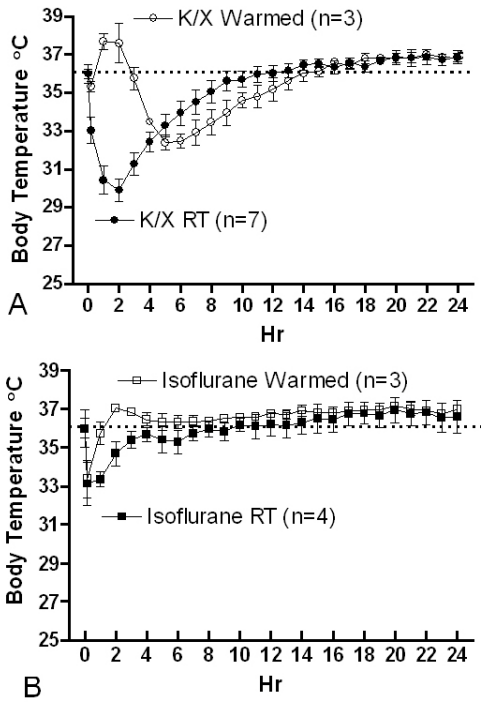

Figure 1. Mice were subjected to sham surgery with either ketamine\xylazine anesthesia (panel A) or isoflurane anesthesia (panel B.). Panel A, ketamine\xylazine anesthesia induced significant hypothermia. Isoflurane also induced hypothermia, but it was to a much lesser degree. The group of mice which are indicated as warm were placed in a warm cage for one hour immediately after surgery. One-hour of warming corrected perioperative hypothermia which is particularly dramatic in panel A. Each value is the mean ± standard error the mean for the indicated number of mice.

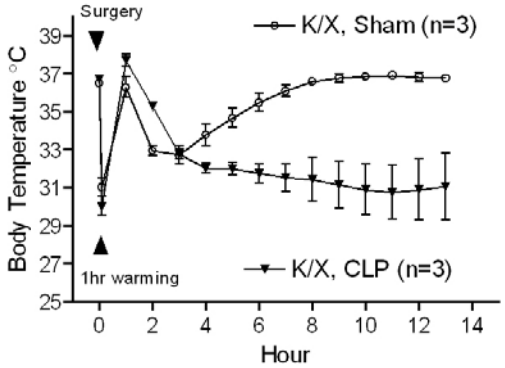

Figure 2. Temperature alterations in sham surgery in the cecal ligation and puncture. Under ketamine\xylazine anesthesia mice which subjected to sham surgery or sepsis induced by cecal ligation and puncture. Both groups of mice had one-hour of perioperative warming to correct the hypothermia. The anesthesia induced hypothermia in the first four to five hours was easily corrected by perioperative warming. However, as the sepsis evolves, CLP mice had significantly lower body temperatures compared to sham operated mice. Each value is the mean ± standard error the mean for the indicated number of mice.

The temperature response to sepsis becomes manifest at a later time point and was examined in mice who merely had sham surgery compared to those subjected to cecal ligation and puncture as displayed in Figure 2. On the basis of these observations, the hypothermia observed in the first five hours is almost certainly due to the anesthesia. However, beginning at about five hours sepsis induced hypothermia manifests itself. This statement is made based on the differences in the temperature curves in the sham operated animals compared to those developing the septic response. Presented in figure 2 is detailed analysis of the early temperature changes after sham surgery compared to CLP surgery. The initial hypothermia induced by the combination of sepsis and anesthesia is more profound than that induced by the anesthesia alone. There are several important observations about these studies. First, at the time of surgery there is rapid induction of hypothermia. The first time point on the curve was taken prior to anesthesia, and the second time point was immediately at the conclusion of surgery. Both of these temperatures were measured with a temperature probe placed on the skin while the rest of the measurements were done with the implanted minimitters. We have previously published that there is excellent correlation between these two different methods for measuring body temperature (35), so there is little reason to believe that the sudden drop in body temperature is solely due to differences in the techniques for measurement. Second, this graph nicely shows that the perioperative hypothermia may be easily corrected. Third, the body temperatures of the animals begin to diverge at about four to five hours. Therefore, anything prior to five hours is most likely due to the anesthetic action while temperature alterations beyond five hours represent part of the physiologic response to sepsis.

At the conclusion of one-hour of warming, either the sham mice or mice with lethal cecal ligation and puncture had near normal body temperatures which is more closely detailed in Figure 3. Therefore, the protocol will correct the perioperative hypothermia, whether the mice had only sham surgery or cecal ligation and puncture induced sepsis. While this initial warming would correct the peri-operative hypothermia, it did not prevent the subsequent sepsis induced drop in body temperature. Specifically, 12 hours after sham surgery or lethal cecal ligation and puncture, those mice with lethal CLP exhibited profound hypothermia while the sham operated mice had a normal body temperature (Figure 4). The normal body temperature occurred whether the mice had the initial 1 hour warming period or were merely maintained at room temperature. Interestingly, in a clinical study 1 hour of warming with forced air was better at preventing core body hypothermia compared to conventional treatment (10).

These data clearly demonstrate that it is possible to modulate the perioperative hypothermia by external warming procedures. What remained to be determined was whether the correction of the perioperative hypothermia would result in improved survival. For these studies, 249 mice were subjected to cecal ligation and puncture. Of these mice, 154 had correction of the perioperative hypothermia using the protocol described for warming the

Table 2. Improved mortality with correction of perioperative hypothermia

Group	# mice subjected to CLP	# alive at 7 days	% survival
Warmed	154	103	67%
Room Temperature	95	50	53%

Correcting perioperative hypothermia results in improved survival in mice with who are developing sepsis

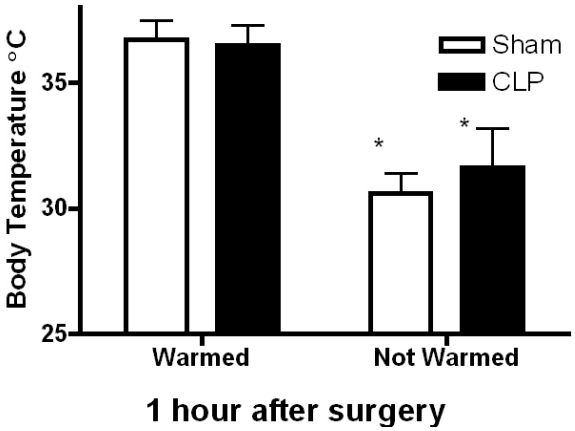

Figure 3. Body temperature 1 hour after surgery. Either sham surgery or CLP was performed and implantable radiotransmitters placed at the time of surgery. Mice were either warmed (placed in a cage with at 35°C) or not warmed (maintained at room temperature). Temperature was recorded 1 hour after surgery, at the conclusion of the warming period. Warming either the sham or the CLP mice maintained the body temperature near normal, while those mice not warmed had lower body temperatures. There was no difference in the temperatures between the CLP or the sham mice. Each value is the mean ± SEM for 4 to 8 mice. * = $p<0.05$ compared to the warmed groups by Student-Newman-Keuls.

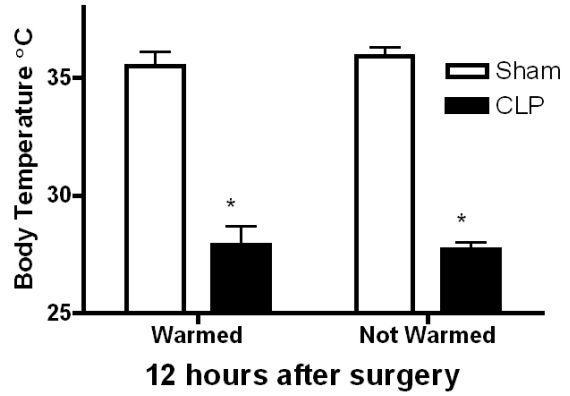

Figure 4. Body temperature 12 hours after surgery. Either sham surgery or CLP was performed and implantable radiotransmitters placed at the time of surgery. Mice were either warmed (placed in a cage with at 35°C) or not warmed (maintained at room temperature). Temperature was recorded 12 hours after surgery. Hypothermia was induced by CLP-induced sepsis in mice, and the body temperature at 12 hours was not affected by prior warming. In contrast, in sham operated mice hypothermia was not observed at 12 hours. Each value is the mean ± SEM for 4 to 8 mice. *=$p<0.01$ sham compared to CLP.

mice while 95 are maintained at room temperature. Table 2 shows that the end of seven days, there was less mortality in those mice who are warmed compared to those mice were not warmed.

It should be noted that reports have been published that hypothermia reduces the inflammatory response and improves survival in response to lethal endotoxin injection (36). Another report showed that hypothermia could reduce the pulmonary inflammatory response to endotoxin (37). However, lethal endotoxemia is not the same as sepsis and there are significant differences in the inflammatory response in these 2 conditions (8). Thus, it is not appropriate to draw conclusions about the beneficial effects of hypothermia on sepsis only on the basis of endotoxin studies.

There have been two other articles which have evaluated the effects of hypothermia of the outcome in sepsis (38, 39). These articles were written from the perspective of the impact of cooling prior to the onset of sepsis. They sought to specifically address the clinical issue of potential negative effects when using global hypothermia for treating ischemic events since previous reports indicated that hypothermia will improve outcome from either cardiac or cerebral ischemia (40, 41). For the studies in rodents with sepsis, the rats were chilled by externally placing ice bags to maintain a core body temperature of approximately 32°C. Sepsis was then instituted with a human fecal inoculum and the rats were treated with antibiotics and fluid resuscitation. The authors correctly point out that this animal model is more clinically relevant because the appropriate treatment is given. Similar to our studies, the rats which had the perioperative hypothermia had a significantly worse outcome compared to those who are maintained at normothermia.

5.3. Mechanisms responsible for improved survival

A significant advantage for performing sepsis experiments in experimental animals is that experiments may be designed to address mechanisms. For example, blood samples or tissue samples may be collected at specific time points to attempt to determine whether there are specific changes responsible for the improved survival. In this regard, the studies mentioned (33, 38, 39) above provide some significant insights. While these previous studies are not directly comparable there are important similarities such as including the use of antibiotics and fluid resuscitation. Important differences between the two studies include differences in the times for sampling to measure cytokines, differences in the antibiotic regimens, and one study was performed in rats while another was in mice. In one of the rat studies, hypothermia had significantly lower levels of IL-6 which were measured one hour after the onset of sepsis (39), while another had

increased levels of IL-6 (38). One of the potential issues with understanding these data are the impact of co-variates on the IL-6 levels. Specifically, hypothermia is associated with increased deaths and numerous studies have indicated that septic animals with higher levels of IL-6 have a substantially increased mortality (42). We separated the mice into those who were alive and those who were dead and then in these groups compared the IL-6 levels in those with hypothermia and normothermia. In both the alive and the dead animals, hypothermia is associated with higher levels of IL-6 (33).

The circulating numbers of neutrophils is also an important prognostic sign in sepsis and mice with higher levels of neutrophils have a better outcome (42). Correction of the perioperative hypothermia did result in a slight increase in the number of circulating neutrophils (33). Additionally, in the rat studies with mild hypothermia and sepsis, administration of exogenous granulocyte colony stimulating factor resulted in improved survival (38).

6. FUTURE PERSPECTIVES

Some aspects of these studies are easily defined and consistent across the different studies. Hypothermia impairs the host response to infection and results in increased surgical wound infections in patients (29). In experimental animal models, perioperative hypothermia also predisposes the animal to a more lethal outcome in response to a systemic infection (33). Consequently, surgical and anesthetic practices which help prevent perioperative hypothermia may provide benefit to the patients. The precise mechanisms of how peri-operative hypothermia alters the immune response to result in increased infections are not well understood at this time.

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