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Does Close Temperature Regulation Affect Surgical Site Infection Rates?

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Keywords

• Intraoperative hypothermia • Surgical site infection • Surgical quality indicators

Key points

- Intraoperative temperature regulation is an increasingly important measure of surgical quality because of its association with surgical site infections.
- Several known biological effects support the observed clinical association between hypothermia and infection.
- Current clinical evidence challenges discrete thresholds for temperature control but supports rewarming and temperature monitoring.

INTRODUCTION

Close intraoperative temperature regulation has increasingly become part of the definition of high-quality surgical care over the last 2 decades. Seminal research at several centers showed that decreased body temperature during surgery is associated with increased total oxygen consumption [1], increased cardiac morbidity [2], increased coagulopathy [3], and increased surgical site infections (SSIs) [4,5]. As evidence for enhanced temperature control has accumulated, multiple health care quality efforts have applied these findings to regulatory interventions. Since 2006, maintenance of normothermia for patients has been part of the Surgical Care Improvement Project (SCIP) [6], a mandatory joint reporting scheme operated by the Joint Commission and the Centers for Medicare and Medicaid Services. The 2 measures, SCIP INF-10 and SCIP

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INF-7 (the latter measure is now retired and is used only for patients having colorectal surgery), require documentation of the use of a forced-air warming device in the operating room or monitoring of intraoperative temperature with minimum end-of-case temperature of 36.0°C for patients without documentation of a warming device. With the increased quality incentives under the US government's 2010 Patient Protection and Affordable Care Act, these quality metrics have become increasingly important to the ongoing operation and financial bottom line of US medical centers.

However, intraoperative temperature control requirements as found in national regulations and their application to surgical practice may not be aligned appropriately with current evidence. Overall, new evidence has mounted that increased compliance with surgical quality measures has not led to a reduction in SSIs [7]. Specific quality measures such as temperature control are now also being scrutinized more closely. The historical examination of temperature control began with observations of the association of SSIs in the absence of rewarming interventions. Although these findings provided early evidence of the importance of temperature, more recent evidence with improved methodologies has challenged this consensus. The 36.0°C target has been found to be less dichotomous than was previously thought.

This article assesses the conventional understanding of close intraoperative temperature control and specifically how the historical consensus may need to be revised in light of more recent findings. It begins by reviewing the physiologic basis from which clinical studies evolved and then shows how those principles were tested over the years through various clinical approaches.

PATHOPHYSIOLOGY PRINCIPLES

The importance of temperature for biochemical processes is well understood and the human body's physiologic mechanisms are optimized for a narrow temperature range around 37°C. Physiologic disturbances worsen as the body cools or warms significantly (±0.2°C) from this core mean temperature [8]. For hypothermic conditions, alterations of normal physiology include increased total oxygen consumption, induced coagulopathy, and immune system dysfunction.

Increased total oxygen consumption and decreased peripheral perfusion

In the intraoperative interval, the use of general anesthesia inhibits normal behavioral defenses to hypothermia, and thus requires complete autonomic regulation of core body temperature. Hypothalamic thermoregulation for hypothermia is a well-understood process of stepwise mechanisms that results from dispersed cold-temperature receptors triggering systemic vasoconstriction and shivering [8]. Vasoconstriction directly impairs oxygen delivery to tissue, and shivering has been shown to increase metabolic oxygen demands by 40% to 300% [1,9]. However, neither of these mechanisms is adequate to reestablish normothermia, even under normal physiologic circumstances. Thermoregulatory shivering in particular continues to increase metabolic demands but never achieves its goal of increasing core body temperature [10].

Induced coagulopathy

Among surgeons, perhaps the best understood consequence of hypothermia is coagulopathy. Much of this well-documented recognition of hypothermia-induced coagulopathy comes from the coagulopathy seen in patients with trauma even when adequately resuscitated with appropriate blood products. Hypothermia-induced traumatic coagulopathy is a major complication that has been associated with the 100% mortality seen in patients with trauma with temperature on presentation of less than 32°C versus 23% mortality in nontraumatic hypothermia [11,12].

The last 2 decades have seen a significantly greater understanding about the underlying physiologic mechanisms of trauma-induced coagulopathy and its relationship with hypothermia. Early studies showed significant alterations in platelet function and clotting factor activity with changes in pH and temperature [13,14]. Further research showed that low temperature alone produced a characteristic set of changes (Fig. 1) [15,16]. Although the hypothermia component of trauma-induced coagulopathy is complex and multifactorial [17–19], the most important physiologic derangements seem to be related to platelet dysfunction directly rather than altered enzymatic activity [17,19].

In the most well-designed studies, enzymatic function (measured by prolonged clotting time and activated partial thromboplastin time) were minimally affected by the typical 3°C to 5°C temperature change seen in traumatic hypothermia. In contrast with platelet activation (ie, bleeding time), platelet aggregation and adhesion were decreased by 40% with a similar temperature change [17]. This latter finding better correlated with the coagulopathic changes seen

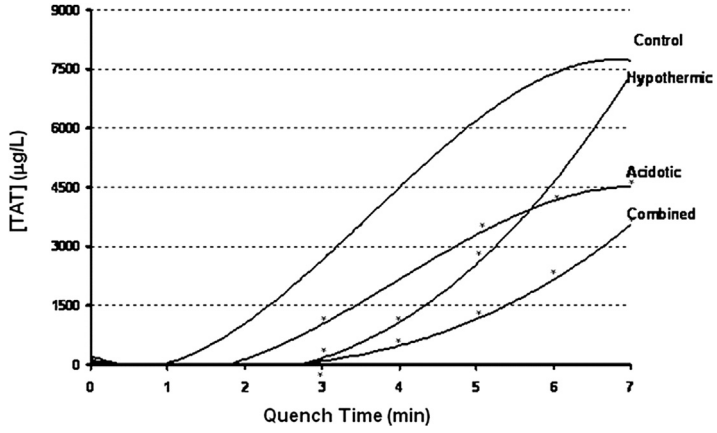

Fig. 1. Thrombin-generation kinetics with alterations in temperature and pH. Compared to controls, hypothermic and acidotic environments both independently impair thrombin generation as measured by the concentration of thrombin-antithrombin complex (TAT). (*From* Martini WZ, Pusateri AE, Uscilowicz JM, et al. Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma 2005;58(5):1002–9; with permission.)

in trauma-induced coagulopathy and suggested that platelet dysfunction rather than activation was the major causative agent.

Showing the association between hypothermia and coagulopathy in more controlled settings than the trauma bay has been difficult because of the limited temperature extremes in elective surgical procedures. Furthermore, routine coagulation studies are run at optimum body temperature, obscuring potential underlying coagulopathies in elective surgical cases [20]. However, small clinical studies have shown evidence of hypothermia-induced coagulopathy and its consequences. For example, Schmied and colleagues [3] found that total hip arthroplasties typically have an additional 500 mL of blood loss when randomly assigned to a target temperature of 35.0°C versus 36.6°C. A recent meta-analysis of the combined work to date found a 16% increase in blood loss and a 22% increase in the relative risk of requiring a transfusion in patients who average approximately 1°C less than the 36°C threshold [21]. This amassed evidence suggests that hypothermia-induced coagulopathy is not only a real, independent phenomenon but that it has observable clinical consequences for patients as well.

Reduced immune response

More is also being learned about effects of hypothermia on the immune system. Although the diffuse effect and complexity of immune activation and feedback pathways have impeded thorough clinical studies of low body temperature and immune system alterations, basic animal models have shown convincing evidence of global effects. For example, guinea pigs have a decreased ability to mount an immune response when treated with a period of hypothermia before being introduced to an *Escherichia coli* dermal challenge [22]. Increasing evidence suggests that hypothermia induces multiple derangements of the host immune response (Fig. 2). Hypothermia has been shown to dull the migration and activation of leukocytes and lymphocytes in both in vitro and clinical experimental models [23–25]. More recently, investigators using advanced immunologic laboratory techniques have further elucidated impaired surface antigen presentation and decreased proinflammatory tumor necrosis factor alpha clearance for in vitro monocytes from healthy volunteers [26]. Although specific mechanisms remain to be further explored, the collective evidence to date suggests that hypothermia induces widespread and significant changes to the host defenses, particularly those of the innate immune response.

PRINCIPLES APPLIED TO SURGICAL PRACTICE

The physiologic impairments of intraoperative hypothermia discussed earlier are important, but their relevance to SSIs gives each a new critical urgency to the modern practice of surgery. The working understanding behind the biological factors contributing to SSIs stems from early work that developed the concept of the decisive period when the ultimate trajectory of these SSIs is thought to be determined. The fundamental finding of these early efforts was that, although SSIs rarely presented until late into the postoperative period, the infectious nidus that established these late infections was typically

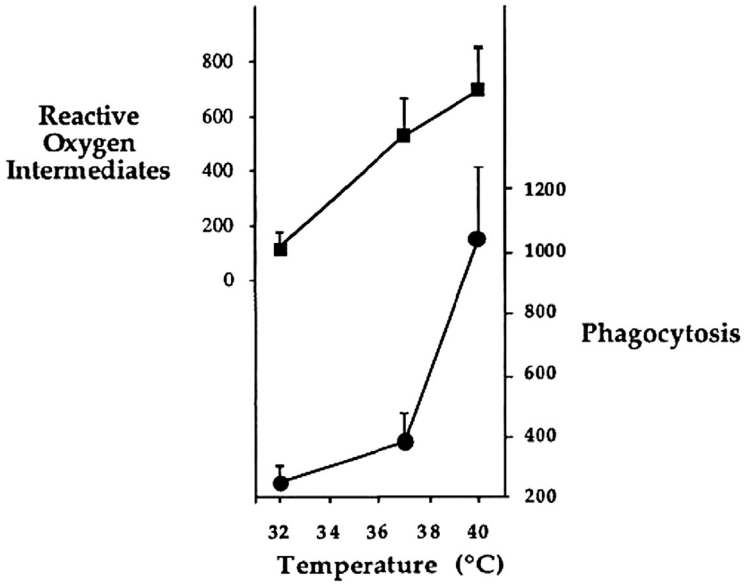

Fig. 2. Polymorphonuclear leukocytes from 10 healthy (normothermic) subjects were incubated at different temperatures. At 0°C, reactive oxygen intermediate production was 31 ± 5 mean fluorescence units and phagocytic capacity was 3 ± 3 mean fluorescence units. Both functions increased significantly at higher temperatures. Data are presented as mean ± standard deviation. (*From* Wenisch C, Narzt E, Sessler DI, et al. Mild intraoperative hypothermia reduces production of reactive oxygen intermediates by polymorphonuclear leukocytes. Anesth Analg 1996;82(4):810–6; with permission.)

established during surgery [27]. The working understanding of SSIs has since focused on preventing these source footholds (eg, perioperative antibiotic prophylaxis and surgical technique). Intraoperative hypothermia is an attractive target as a modifiable risk factor given that its physiologic effects occur in the midst of this decisive period of high infection risk.

All of the physiologic mechanisms described earlier have clear causal effects on impaired wound healing and thereby affect the risk of SSI (Fig. 3). An absolute requirement of wound healing is effective quality and quantity of tissue perfusion. Increased oxygen consumption decreases oxygen tension at surgical wound edges, which has a known correlation with poor wound healing [4,28]

Fig. 3. Contributions of hypothermia-induced physiology to wound infections.

and postoperative infection [29]. Coagulopathy and the resulting need for further blood transfusions has both a direct immunosuppressive effect [30–33] and an indirect effect of decreasing peripheral tissue perfusion. In addition, a decreased innate immune response eases a virulent organism's ability to establish that critical intraoperative foothold, and decreased antigen presentation has been shown to correlate directly with infection [34].

EVIDENCE BASE OF CLINICAL PRACTICE

Largely driven by the basic science and physiologic principles outlined earlier, the last 2 decades have seen a host of clinical studies hoping to improve hypothermia prevention strategies and thereby reduce SSI rates. The earliest and most far-reaching of these studies was a randomized controlled, double-blind trial performed by Kurz and colleagues [4] in 1996. The study followed 200 patients undergoing elective colorectal procedures at 3 Austrian hospitals over a 2-year period. At anesthesia induction, each patient was randomized to one of 2 temperature management groups with an actively warmed, stringent normothermia group targeted to 36.5°C versus a nonwarmed, permissive hypothermia group targeted to 34.5°C. The stringent normothermia group's SSI rate was 6% versus 19% in the permissive hypothermia control group ($P = .009$). These dramatic results not only rapidly changed intraoperative warming practices in much of the world but this is still the predominant study cited by regulatory bodies when crafting intraoperative temperature control guidelines [6].

Although far-reaching, Kurz and colleagues' [4] study had limitations. Some of these limitations were intentional elements that were initially designed to balance the effects of randomization to either of the two patient groups. For example, the study team went to elaborate lengths to ensure that the treatment group's warmed, forced-air intervention appeared nearly identical to a room temperature, forced-air control that included working blowers and cardboard shielding for display panels. However, it has been noted that such placebo devices for the control group may have inadvertently exacerbated typical intraoperative hypothermia by having ambient air blown across the patients' skin during the procedure [35]. Causality concerns have also been raised around Kurz and colleagues' [4,36] finding associating hypothermia with increased antibiotic use, increased length of stay, and higher rates of blood transfusions. Although it is possible that such events were the result of an intraoperative hypothermic episode, this may also suggest that sicker patients were more likely to be hypothermic during surgery. These events also have long-standing recognition for their independent contribution to SSI [36].

Another major study was reported from the United Kingdom in 2001 that sought to expand previous findings to a broader array of surgical patients. This study was designed to determine whether the findings of Kurz and colleagues [4] could be expanded from longer, clean-contaminated cases to shorter, clean cases. The major novel intervention of Melling and colleagues [37] was the introduction of preprocedure warming to ensure a circulatory stimulating

effect even with a short case length. Similarly to Kurz and colleagues [4], Melling and colleagues [37] found a 14% wound infection rate in nonwarmed patients and a 5% infection rate in those who received any form of warming ($P = .001$).

Although the findings of Melling and colleagues [37] further broadened the use and diversity of perioperative warming strategies, the study has been viewed with caution. First, the study was performed at a single British health institution, which may limit its universal applicability. Although it contained more than double the number of operative cases assessed by Kurz and colleagues [4] (n = 421 vs n = 200), these procedures were exclusively clean cases with a much lower effect size and therefore less imminent relevance to surgical practice. There were also concerning omissions and aberrant findings in the data. For example, mean temperatures were not recorded for each group [38]. It also seems that an unusually high reported infection rate for clean cases (14% vs 2% to 4% of conventional estimates) was caused by the atypical definition used by the investigators to categorize an SSI, which even included home journaling as evidence for a positive finding [39].

One of the many ongoing criticisms of these two studies by Kurz and colleagues [4] and Melling and colleagues [37] concerns the poor correlation of these reported results and their methodological idiosyncrasies with observational data provided by other research groups. The article by Barone and colleagues [36] was one of the first early articles to amass observational evidence that was both more consistent with typical surgical practices and also challenged the clear association between hypothermia and SSIs. The investigators not only found SSIs to be insignificantly different between normothermic and hypothermic patients but they also took issue with many of the secondary findings of the two aforementioned studies. In particular, Barone and colleagues [36] challenged the randomization of the 2 Kurz and colleagues [4] patient groups based on Kurz and colleagues' [4] own institutional data that showed no difference in blood transfusions, days of antibiotics, length of stay, and days to advance diet between high and low intraoperative temperature groups. Barone and colleagues [36] noted that these variables are important and were not universally well controlled for by Kurz and colleagues [4], suggesting that differing treatments of the two patient groups that went beyond temperature control could explain the difference in SSI rate. However, Barone and colleagues' [36] study had its own limitations. Barone and colleagues [36] observed that nearly a third of their institutions' patients unintentionally become hypothermic, which could suggest an institutional bias away from normothermia. They also used an extreme definition of hypothermia that may have skewed the hypothermic subsets of patients that were included in the analytical group [35].

By the early 2000s, the amassed evidence began to split into 2 separate clinical arguments. First, most of the support for intraoperative hypothermia prevention did not concern hypothermia directly but instead showed evidence that intraoperative warming prevented SSIs. Second, the major studies discussed earlier and their active supporters had still not definitively shown an

independent correlation between intraoperative core temperature and SSIs. Lehtinen and colleagues [40] used the enhanced capabilities and data collection of the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) to address these outstanding issues. The investigators conducted a case-control observational cohort on 469 patients in their institution's NSQIP database. This study used the diverse breadth of NSQIP patients to analyze a patient population that was between the high-infection-risk colorectal patients of Kurz and colleagues [4] and the low-infection-risk patients of Melling and colleagues' [37] clean case population. It also was able to use internal medical records to obtain perioperative temperature readings, antibiotic usage, and glucose management. With these mitigated methodological underpinnings, Lehtinen and colleagues [40] showed no independent association between perioperative hypothermia and SSIs ($P = .90$). The investigators found that normothermia correlated with an increased risk of SSI, which they attributed to the increased perioperative temperatures of emergency surgery and dirtier cases, both of which likely went to the operating room with higher-than-average perioperative temperatures from systemic inflammatory response syndrome physiology.

Prior studies showed the benefits of intraoperative warming for infectious outcomes, and thus led to conventional thinking that higher temperatures were better than lower temperatures. This thinking has been repeatedly confirmed, most recently in both large, prospective NSQIP-like databases [41] and focused, single-institution, single-specialty cohort studies [42]. This rationale was largely the stimulus for the current pay-for-performance intraoperative temperature requirements now popular in US surgical practice [6]. Most recently, Hendren and colleagues [42] showed the ongoing resilience of quality measures like SCIP's postoperative hypothermia requirement, in which the investigators found it to be one of a few significant predictors of SSI in a multi-institutional study using a large statewide patient cohort.

Although Lehtinen and colleagues' study had its own analytical and methodological limitations, [40,43] largely because of the study being conducted in an era with strict temperature control management already in place, this study was one of the first to challenge the conventional, narrow focus on a dichotomous margin between good and bad intraoperative temperatures.

The most recent contribution to the question of intraoperative management comes from 2 of this article's co-authors, who have attempted to reexamine the question of specific intraoperative temperature cutoffs. This work has further developed prior findings while mitigating some of limitations of clinical research in an era of temperature management that does not readily allow randomized controlled trials because of the existing evidence on warming devices. Melton and colleagues [44] again used NSQIP data and linked it with the Cleveland Clinic Foundation Hospital's continuous anesthesia informatics systems. This methodology allowed the comparison of multiple intraoperative temperature measures versus patients' likelihood of developing an SSI. Using a merged database of 1008 total colorectal patients, Melton and colleagues [44]

showed no significant difference between any continuous measure of intraoperative temperature and the incidence of SSI ($P<.05$) (Table 1). Although they are only observational data, these later studies have successfully challenged the paired wisdom of warming devices and intraoperative temperature monitoring.

Like Lehtinen and colleagues' [40] study, Melton and colleagues' [44] observational study is hindered by the post-SCIP era in which the large swings in intraoperative temperature management and the subsequent outcomes noted by Kurz and colleagues [4] are much less frequent. However, there is still enough temperature variation in these 2 latest studies to question whether the specific 36.0°C requirement of existing regulatory policies is worthy of the current impact it has on the surgical care of patients. In particular, Melton and colleagues [44] provide new evidence that marginal differences in

Table 1
Melton and colleagues' [44] independent correlation between SSI and various continuous measures of intraoperative temperature

Temperature measure (°C)	SSI = No (833)		SSI = Yes (175)		
	Mean	IQR	Mean	IQR	*P*
Mean temperature	36.0°C	36.0–36.1°C	36.1°C	36.0–36.2°C	.12
Median temperature	36.0°C	36.0–36.1°C	36.1°C	36.0–36.2°C	.10
Maximum temperature	36.5°C	36.4–36.5°C	36.6°C	36.5–36.7°C	.054
Minimum temperature	35.0°C	34.9–35.0°C	34.9°C	34.7–35.1°C	.84
Initial temperature	35.4°C	35.3–35.4°C	35.3°C	35.1–35.5°C	.67
Final temperature	36.2°C	36.2–36.3°C	36.4°C	36.3–36.5°C	.054
Delta (change in temperature)	0.88°C	0.88–0.97°C	1.0°C	0.86–1.2°C	.13
Area under the curve	8.0°C	8.0–8.1°C	8.1°C	8.0–8.2°C	.34
Absolute minutes at less than the threshold temperature					
37.5°C	165	159–171	197	182–212	<.0001
37.0°C	149	143–154	180	165–195	.0002
36.5°C	126	120–132	143	128–157	.03
36.0°C	69	64–74	67	56–78	.78
35.5°C	34	30–37	29	22–37	.33
35.0°C	7	5–9	7	2–11	.79
34.5°C	2	1–3	2	0–5	.97
34.0°C	0.5	0.2–0.8	0.4	0.0–0.8	.57
Percentage of time at less than the threshold temperature					
37.5°C	99	98–99	99	97–100	.72
37.0°C	90	89–92	91	88–94	.52
36.5°C	77	75–88	74	69–79	.22
36.0°C	43	40–45	36	31–42	.056
35.5°C	20	19–23	17	13–21	.11
35.0°C	4.5	3.5–5.6	3.2	1.3–5.1	.21
34.5°C	1.6	1.0–2.2	1.0	1.1–1.9	.29
34.0°C	0.5	0.1–0.8	0.2	0.06–0.3	.11

Abbreviation: IQR, interquartile range.

From Melton GB, Vogel JD, Swenson BR, et al. Continuous intraoperative temperature measurement and surgical site infection risk. Ann Surg 2013;258(4):606–12; with permission.

temperature variation have no significant impact on surgical outcomes. Clear evidence supports the current consensus that a cold patient is likely to have worse surgical outcomes [41,45–47], but as yet there are no definitive studies that show the validity of a stringent 36.0°C temperature requirement.

SUMMARY

The argument for close temperature control, to which regulatory bodies have held health systems in an effort to reduce the burden of hospital-acquired infections, is not fully supported by current evidence. The literature is complex on the topic, and overinterpretation of historical data supporting close temperature regulation does not preclude an important recognition of these early works' contribution to high-quality surgical care. Avoidance of hypothermia through the regular use of active rewarming should be a routine part of safe surgical care. The biochemical basis of emphasizing temperature regulation is sound, and ample evidence shows the frank physiologic derangements seen when biological processes occur at suboptimal temperature. It is also recognized that patients tend to do better when warmed during the perioperative period, suggesting that warming devices are an important and essential adjunct to good perioperative care. Clinicians, researchers, and policymakers must be careful in how they apply these well-supported findings to process metrics in an era of limited resources with increasingly stringent quality guidelines and outcomes measures. Discrete temperature targets in current measures are not supported by the existing literature. Not only do these targets artificially anchor clinicians to temperature values with an inadequate scientific basis but they demand intensive resources from health institutions that could potentially be better used on quality requirements with stronger evidence of their ultimate effect on patient care.

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