

Elevated Thermostatic Setpoint in Postoperative Patients

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Background: **The mechanism and clinical relevance of increased core temperature (Tc) after surgery are poorly understood. Because fever is used as a diagnostic sign of infection, it is important to recognize what constitutes the normal postoperative thermoregulatory response. In the current study the authors tested the hypothesis that a regulated increase in Tc setpoint occurs after surgery.**

Methods: **The authors prospectively studied 271 patients in the first 24 h after a variety of vascular, abdominal, and thoracic surgical procedures. Tc measured in the urinary bladder, skin-surface temperatures, thermoregulatory responses (vasoconstriction and shivering), and total leukocyte counts were assessed. In a subset of 34 patients, plasma concentrations of tumor necrosis factor, interleukin (IL)-6, and IL-8 were measured before and after surgery.**

Results: **In the early postoperative period, the maximum increase in Tc above the preoperative baseline averaged 1.4 ± 0.8°C (2.5 ± 1.4°F), with the Tc peak occurring 11.1 ± 5.8 h after surgery. Fifty percent of patients had a maximum Tc greater than or equal to 38.0°C (100.4°F) and 25% had a maximum Tc greater than or equal to 38.5°C (101.3°F). The progressive postoperative increase in Tc was clearly associated with cutaneous vasoconstriction and shivering, indicating a regulated elevation in Tc setpoint. The elevated Tc was associated with an increased IL-6 response but not with leukocytosis. Maximum postoperative Tc was positively correlated with duration and extent of the surgical procedure.**

Conclusions: **A regulated elevation in Tc setpoint (fever) occurs normally after surgery. The association between Tc elevation, extent and duration of surgery, and the cytokine response suggests that early postoperative fever is a manifestation of perioperative stress. (Key words: Hyperthermia; surgery; thermoregulation.)**

CORE temperature (Tc) is often elevated after surgery, but the mechanism and clinical relevance of postoperative fever are unclear. Because fever is used as a diagnostic sign of infection, it is important to recognize what constitutes the "normal" postoperative Tc response. Although traditional definitions of fever (38.3–38.5°C) appear to correlate with infection in medical patients,[1] febrile surgical patients frequently have no identifiable source of infection.[2,3]

Although pulmonary atelectasis has classically been described as the cause of postoperative fever, more recent evidence refutes this theory[4] and suggests that cytokines play a role.[5,6] Stress-induced fever has been shown to occur in both humans and animals,[7] and it is possible that postoperative changes in body temperature are a manifestation of the perioperative stress in response to tissue injury. Because fever is often the earliest and most easily detected sign of infection in the surgical patient, it is important that the mechanism and clinical implications of postoperative Tc elevation be clearly defined.

To define the normal postoperative thermoregulatory response, we assessed Tc, thermoregulatory responses (vasoconstriction and shivering), cytokines, and the leukocyte response after major surgical procedures. We tested the hypothesis that true fever (*i.e.*, a regulated increase in Tc) is the normal response after surgery.

Methods

Patient Population

After obtaining approval from the Johns Hopkins Hospital Committee on Clinical Investigations and written informed consent, 271 patients undergoing elective abdominal, noncardiac thoracic, or major vascular surgery were enrolled in the study. These patients concomitantly participated in a clinical trial on cardiac outcomes, the results of which have been published elsewhere.[8] Patients were excluded if preoperative Tc was greater than or equal to 38.0°C, as measured by infrared tympanic thermometry (Thermoscan, San Diego, CA). Patients with a known source of infection were not enrolled.

Study Design

Intraoperative anesthetic technique was determined by the nature of the surgical procedure. Most patients undergoing abdominal, thoracic, or carotid surgery received a balanced general anesthetic with a combination of thiopental sodium, an opioid, a neuromuscular blocker, nitrous oxide, and isoflurane or enflurane. The trachea was intubated during surgery and was extubated in the majority of patients before they left the operating room. Postoperative analgesia in these patients was achieved with morphine sulfate given intravenously by patient-controlled analgesia. Epidural anesthesia was used primarily for patients undergoing lower-extremity vascular procedures and was delivered using lidocaine and/or bupivacaine to achieve a sensory block between the sixth and tenth thoracic dermatomes. For these pa-

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tients, postoperative analgesia was achieved with bupivacaine–fentanyl given epidurally. Thermal management was dictated by protocol during surgery.[8] Approximately one half of all patients were actively warmed during surgery.

Postoperatively, all patients were admitted to either the surgical intensive care unit or the postanesthetic care unit for an overnight stay. Patients were not actively warmed in the postoperative period but were covered with one or two layers of cotton blanket, according to their level of thermal comfort as assessed by the nursing staff. Mean ambient temperature during the initial postoperative 24 h was 22.8 ± 2.2°C.

Body Temperature Monitoring and Cytokine Measurement

All temperatures were monitored in all patients with thermocouple probes connected to a 16-channel electronic thermometer (Iso-Thermex, Columbus Instruments, Columbus, OH) and recorded onto a laptop computer at 5-min intervals for the first postoperative 24 h. Tc was measured using thermocouples in the urinary bladder (Mon-a-therm; Mallinckrodt Inc., St. Louis, MO). Skin-surface temperatures were measured on the anterior surface of the forearm and on the tip of the index finger opposite the nailbed using adhesive thermocouples with foam backing insulation (Mon-a-therm). The degree of peripheral vasoconstriction was assessed by calculating the forearm minus the fingertip skin-surface temperature gradient.[9] An increase in gradient indicated vasoconstriction. All temperature data were reviewed by an investigator to detect and eliminate erroneous artifact. Shivering was assessed and recorded every hour by trained clinical nurses using a four-point scale,[10] with a score greater than zero defined as the presence of shivering. Total leukocyte count was measured in arterial blood samples (Sysmex SE-9500; TOA Medical Electronics, Tokyo, Japan) preoperatively and on the morning of the first postoperative day in all 271 patients.

Diagnostic laboratory testing for postoperative infection was dictated by routine criteria for the surgical intensive care unit of the Johns Hopkins Hospital. Cultures of urine, sputum, and blood, as well as x-ray examination of the chest, were obtained when the attending physician determined that there were clinical signs or symptoms of infection. Cultures positive for pathogenic organisms were considered positive evidence for infection.

Arterial blood samples were taken for cytokine analysis from a subset of 34 consecutively enrolled patients. Plasma concentrations of tumor necrosis factor and interleukin (IL)-6 were measured by bioassay, and of IL-8 were measured by enzyme-linked immunosorbent assay preoperatively and at 0, 1, 3, and 14 h postoperatively.

Table 1. Characteristics of the Patients

Demographic Data (n = 271)	
Age (yr)	70 ± 6
Sex	
Male	152 (56)
Female	119 (44)
Surgical procedure	
Abdominal	125 (46)
Thoracic	35 (13)
Vascular	111 (41)
Diabetes	41 (15)
Hypertension	182 (67)
Cigarette smoking	135 (50)
Weight (kg)	74 ± 15
ASA classification	
II	24 (9)
III	215 (80)
IV	32 (12)
Duration of Surgical Procedure (hr)	3.6 ± 1.1
Body Temperature Data (n = 271)	
Preoperative core temperature (°C)	36.6 ± 0.6
Immediate postoperative core temperature (°C)	36.0 ± 1.0
Postoperative maximum core temperature (°C)	38.0 ± 0.7

Plus–minus values are mean ± SD. Dichotomous data are number of patients with percentages in parentheses.

ASA = American Society of Anesthesiologists.

Statistical Analysis

The demographic data were analyzed using the Student *t* test and chi-square analyses. The distribution of the preoperative Tc and postoperative maximum Tc in the first postoperative 24 h were defined by median, quartile, and percentile values. The relation between Tc and leukocyte count was analyzed by simple linear regression. The cytokine response was compared in patients with Tc above and below the traditional definition of postoperative fever (38.5°C) using analysis of variance for repeated measures. Predictors of maximum Tc were first determined by univariate testing. Variables tested were age, gender, cigarette smoking, diabetes mellitus, history of hypertension, β-adrenergic blockade, surgical procedure, anesthetic technique, intraoperative thermal management, and duration of surgical procedure. Multiple linear regression with backward elimination[11] was then used to identify independent predictors of maximum Tc. Data are reported as mean ± SD, and *P* less than 0.05 was used to define significance.

Results

Because of the nature of the surgery, the population was elderly with a relatively high incidence of coexisting disease (table 1).

Preoperative and Postoperative Core Temperature

The maximum Tc in the initial 24-h postoperative period was normally distributed and was greater than preoperative Tc (fig. 1). The median and mean maximum Tc were 38.0°C and 38.0 ± 0.7°C, respectively.

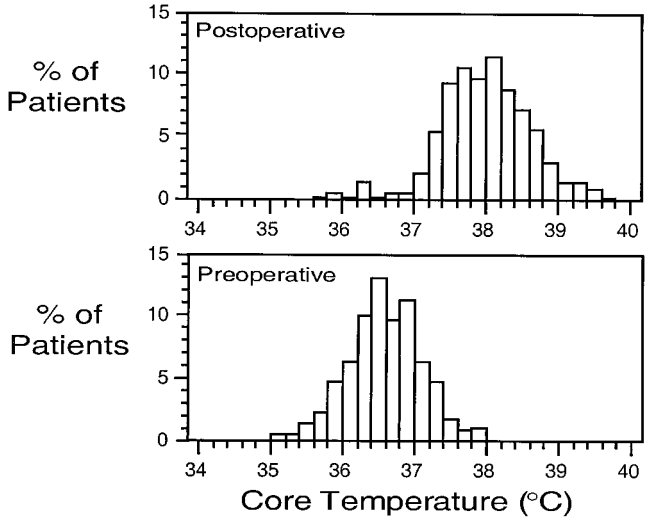

Fig. 1. Histograms illustrating preoperative and maximum postoperative core temperature in the first 24 h after surgery in 271 patients. The data indicate a postoperative shift in the setpoint toward a greater core temperature.

One fourth of all patients had a maximum Tc greater than or equal to 38.5°C, and 10% had a maximum Tc greater than or equal to 38.8°C. The mean Tc maximum was 1.4 ± 0.8°C greater than the preoperative Tc ($P < 0.0001$). Maximum Tc occurred at an average of 11.1 ± 5.8 h after completion of surgery.

Postoperative Thermoregulatory Response

Core temperature decreased significantly during anesthesia and surgery, as expected, resulting from anesthetic-induced thermoregulatory inhibition (fig. 2).[12] Immediately after surgery, Tc progressively increased. This increase was temporally correlated with both the onset of vasoconstriction (an increased forearm skin-surface temperature gradient) and with shivering. Both vasoconstriction and shivering resolved when Tc reached the new setpoint as defined by a stable Tc plateau (fig. 2). The relation between Tc and total leukocyte count in 271 patients was not significant ($r^2 = 0.15$, $P = 0.77$ by linear regression). The leukocyte count was not different in patients with maximum Tc greater than or equal to 38.5°C (11,500 ± 4,500 cells/ml) and less than 38.5 (12,200 ± 4,800 cells/ml; $P = 0.45$).

Cytokines and the Thermoregulatory Response

For 34 patients in whom cytokines were assayed, there was a positive relation between the IL-6 response and the postoperative increase in Tc (fig. 3). The mean IL-6 plasma concentration was twofold to threefold greater in patients with Tc greater than or equal to 38.5°C than in those with Tc less than 38.5°C ($P = 0.01$ for the time X group interaction). Tumor necrosis factor was not related to Tc, and IL-8 was undetectable in most patients.

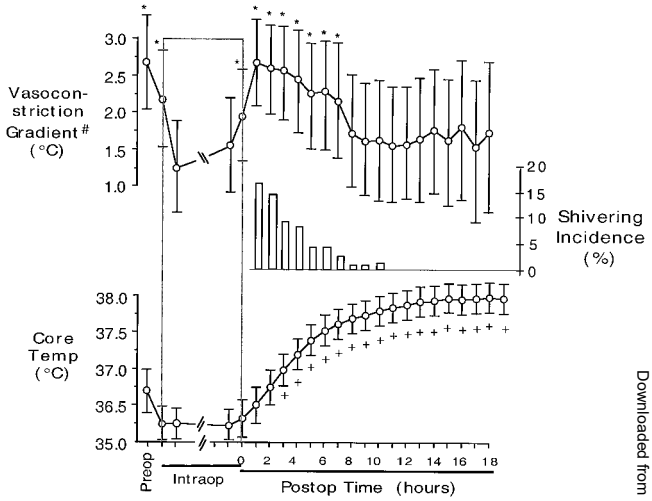

Fig. 2. Core temperature, percent of patients shivering, and vasoconstriction gradient in 271 patients during the preoperative (preop), intraoperative (intraop), and postoperative (postop) periods. The postoperative increase in core temperature is accompanied by shivering and vasoconstriction, both of which diminish as core temperature reaches the new greater postoperative setpoint. The increase in vasoconstriction gradient indicates increased vasomotor tone. #Forearm minus fingertip skin-surface temperature gradient; *$P < 0.05$ *versus* intraoperative vasoconstriction gradient; +$P < 0.05$ *versus* preoperative core temperature.

Predictors of Maximum Core Temperature

Variables associated with a greater maximum Tc by univariate testing were a younger age, type of surgical procedure, and duration of surgical procedure (table 2). The only independent predictors of greater maximum Tc by multivariate testing were type and duration of surgical procedure (table 2). Anesthetic technique and intraoperative thermal management were not independent predictors of maximum Tc. The extent and dura

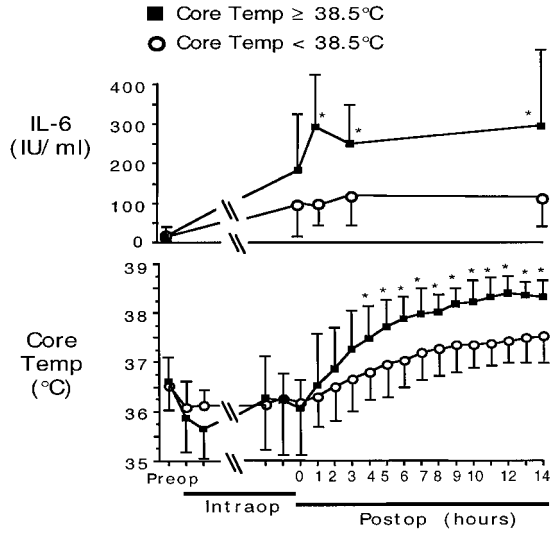

Fig. 3. Preoperative, intraoperative, and postoperative temperature and cytokine data for 34 patients, analyzed by maximum core temperature in the initial 14 h postoperatively. Interleukin (IL)-6 was significantly elevated in patients with core temperature > 38.5°C. *$P < 0.05$ *versus* core temperature < 38.5°C.

Table 2. Univariate and Multivariate Determinants of Maximum Tc

Clinical Variable	Mean Maximum Tc (°C)	*P* Value	
		Univariate	Multivariate
Age ≥ 70 yr (n = 147)	37.9 ± 0.6	0.01	0.13
Age < 70 yr (n = 124)	38.1 ± 0.5		
Sex			
Male (n = 153)	38.0 ± 0.7	0.09	0.58
Female (n = 118)	37.9 ± 0.6		
Smoking history (n = 136)	38.1 ± 0.7	0.052	0.58
No smoking history (n = 127)	37.9 ± 0.5		
Diabetes (n = 44)	38.0 ± 0.4	0.45	0.88
No diabetes (n = 227)	38.0 ± 0.7		
Hypertension (n = 190)	38.0 ± 0.8	0.65	0.26
No hypertension (n = 81)	38.0 ± 0.4		
Preoperative β blocker (n = 79)	38.0 ± 0.4	0.41	0.85
No preoperative β blocker (n = 192)	37.9 ± 0.9		
Surgical procedure			
Abdominal (n = 125)	37.8 ± 0.7		
Thoracic (n = 35)	38.0 ± 0.6	0.02	0.04
Vascular (lower extremity; n = 88)	38.2 ± 0.6		
Vascular (carotid; n = 23)	37.7 ± 0.3		
Duration of surgery*		0.001	0.02
Anesthetic technique			
Epidural (n = 79)	38.2 ± 0.3	0.03	0.37
General (n = 192)	37.9 ± 0.6		
Intraoperative warming			
Yes (n = 130)	38.0 ± 0.6	0.60	0.40
No (n = 141)	38.0 ± 0.7		

Plus–minus values are mean ± SD. Univariate determined by unpaired *t* test, except for duration of surgery, which was analyzed by linear regression.

* No temperature data are given because duration of surgery was analyzed as a continuous variable.

Tc = core temperature.

tion of the surgical procedure was proportional to the maximum Tc in the early postoperative period (table 3).

Only one patient had clinically evident signs of infection in the initial 24 h postoperatively (with positive urine and blood cultures). Maximum Tc was 39.4°C (95th percentile for Tc), and leukocyte count was 10,300 cells/ml for this patient.

Table 3. Mean Maximum Tc and Duration of Surgery by Surgical Procedure

Procedure	Maximum Tc (°C)	Duration of Surgery (h)
Carotid endarterectomy (n = 23)	37.7 ± 0.5	2.1 ± 1.4
Lower abdominal surgery (n = 40)	37.7 ± 0.6	4.1 ± 1.5
Upper abdominal surgery (n = 85)	37.9 ± 0.7	5.1 ± 1.8
Femoral–popliteal bypass (n = 46)	37.9 ± 0.5	4.6 ± 1.2
Thoracic surgery (n = 35)	38.0 ± 0.6	4.2 ± 1.8
Femoral–distal bypass (n = 42)	38.4 ± 0.6	5.7 ± 1.8

Plus–minus values are mean ± SD. $P = 0.001$ by one-factor analysis of variance for difference in duration between surgical procedures.

Tc = core temperature.

Discussion

Surgical patients are subjected to dramatic alterations in body temperature during the intraoperative and postoperative periods.[12] Although much attention has been directed to the complications of intraoperative hypothermia,[8,12,13] elevated Tc in the postoperative period occurs commonly and is poorly understood. Our findings indicate that early postoperative elevation in Tc is a normal response after major surgical procedures that occurs in proportion to the duration of surgery and is associated with elevated levels of IL-6. In addition, this response satisfies the true definition of fever, *i.e.*, regulated increase in Tc setpoint.[5] Historically, fever has been used clinically as a sign of infection, but stress-induced fever is also well recognized,[7,14] and early postoperative fever appears to be a manifestation of perioperative stress.

Classic surgical literature describes pulmonary atelectasis as a contributing factor to postoperative fever.[15,16] However, recent studies fail to show correlation between body temperature and atelectasis in postsurgical patients.[4,17] Infection is an ominous cause of fever in the postoperative patient, but evidence indicates that fever in the postoperative period is neither sensitive nor specific as a clinical sign of infection.[18,19] Depending on the definition of postoperative fever, previous studies have estimated its incidence to be between 13% and 40%.[1–4,19–21] The results of most previous investigations are limited, however, because only intermittent temperature measurements were taken from either rectal or oral sites, both of which are prone to inaccuracy.[24] In addition, previous investigators did not assess the vasoconstriction or shivering responses, and thus the elevated Tc was not shown to be regulated.[25] In our study, Tc was continuously measured in the urinary bladder, which provides a reliable assessment of Tc, and thermoregulatory responses were also measured.

The setpoint for Tc is influenced by endogenous substances, categorized as pyrogens or cryogens, which work by altering the thermoregulatory setpoint in the anterior hypothalamus. Known pyrogens include IL-1, IL-6, tumor necrosis factor, and interferon.[5,26,27] Cryogenic substances include glucocorticoids, arginine vasopressin, and low doses of tumor necrosis factor.[28,29] It is generally accepted that IL-1, IL-8, and IL-10 are not increased after tissue injury and are unlikely to contribute to the postoperative changes in Tc.[30] Although one study found a correlation between IL-6 levels and peak Tc,[6] others have shown poor correlation.[31] Our findings suggest that IL-6 acts as a pyrogen in postsurgical patients and that the magnitude of this response is in

proportion to surgical tissue injury. The effect of endogenous pyrogens is to increase the Tc setpoint in the anterior hypothalamus, probably through increased levels of prostaglandin E2.

Even in the nonsurgical patient, the Tc definition of fever is not entirely clear. Tc varies up to 0.5°C depending on the site of measurement.[24] There is a daily circadian rhythm for normal body temperature in both men and women and a monthly variation during different phases of the menstrual cycle. When the stress and inflammation from trauma and surgery are added to these variables, it becomes difficult for clinicians to agree on a definition of postoperative fever. Our data suggest that the traditional definition of fever used in postoperative patients (Tc $\geq$ 38.5°C) may be too stringent because approximately 25% of all patients meet this criterion.

The incidence of Tc elevation was different among the subcategories of surgical procedures that were included in this study. In general, the procedures with longer surgical incisions and longer duration (*i.e.*, femoral-distal vascular bypass) had the greatest postoperative increase in Tc. Conversely, procedures with shorter incisions and duration (*i.e.*, carotid endarterectomy) has less increase in Tc. These findings suggest that tissue injury (or tissue ischemia during vascular clamping) is related to postoperative inflammation and elevated Tc. The degree of tissue injury and severity of the surgical procedure are proportional to the increased circulating concentrations of IL-6,[32] a known endogenous pyrogen. Other potential mediators of the greater febrile response after more invasive surgery include pain, psychological stress, and the associated catecholamine response.[33,34] These are likely to occur in proportion to surgical invasiveness and have been shown to elicit a pyrogenic response, probably through a β-adrenoceptor mechanism.[35]

An important question is whether postoperative elevations in body temperature represent true fever or alternatively hyperthermia.[36] The answer to this question should guide clinicians in their treatment of the disorder. True fever is an alteration of the thermoregulatory setpoint, which implies a feeling of cold discomfort and active vasoconstriction and shivering until the new setpoint is attained.[27] The treatment of true fever should focus primarily on returning the setpoint toward normal with antipyretics (acetominophen or cyclooxygenase inhibitors). Hyperthermia occurs when heat gain (usually from an exogenous source) exceeds heat loss, resulting in an elevated Tc that is not regulated. The treatment for this condition should focus on active cooling. Our results suggest that increased body temperature after surgery is characteristic of true fever because regulation (vasoconstriction and shivering) to achieve a higher Tc setpoint was demonstrated. Therefore, antipyretics would be preferable to active cooling.

The evaluation of fever in the postoperative period often includes a battery of diagnostic tests to determine the source or to exclude a serious infection. The resulting costs of culturing urine, blood, sputum, the wound, cerebrospinal fluid, and central lines are significant. According to Freischlag *et al.*,[23] the average cost of a fever workup was $278 per febrile patient. These investigators concluded that the routine evaluation of postoperative fever did not alter outcome and was not cost effective. In a 1991 study by Theurer *et al.*,[18] the cost to identify each patient with a positive blood culture was $2,800, and the investigators concluded that in no case did a positive blood culture have a measurable effect on reducing patient morbidity or mortality. Shulkin *et al.*[37] showed that postoperative infection added an average of $12,542 to the cost of a patient's care, and fever without infection added an average of $9,145. These costs were generally incurred through microbiology tests, radiology services, pharmaceutical costs, and hospital room costs. By defining the normal changes in Tc after surgery, the findings of the current study may decrease the cost of postoperative surgical care by decreasing the use of diagnostic laboratory tests for fever workup.

Possible limitations of the current study deserve mention. Because the data were collected in the first 24 h after surgery, the findings are most relevant to the early postoperative period. A greater incidence of infection is well recognized when the duration of follow-up is longer. The clinician should therefore use caution when interpreting fever occurring later in the postoperative course when fever may more likely be associated with infection. It should also be recognized that circadian variation in Tc might have contributed somewhat to postoperative temperature elevation in our study. These rhythmic changes in temperature will occur, regardless of surgery and anesthesia,[38] and are rarely considered in the diagnostic criteria for infection. Further studies would be helpful to determine if criteria for fever should be adjusted in a circadian fashion. Finally, routine surveillance for infection was not used in this study. Therefore, it cannot be assumed that all fevers occurred in the absence of infection. However, it is apparent that fever often occurs in the absence of clinically evident infection.

In summary, patients who undergo major surgical procedures experience a regulated increase in Tc setpoint in the early postoperative period, which fits the classic definition of fever. The average Tc setpoint after surgery is elevated by 1.4°C (2.5°F) above the preoperative baseline. This increased Tc occurs in proportion to surgical duration and is associated with elevated IL-6, suggesting that tissue injury and perioperative stress play a role. By defining the normal thermoregulatory response after surgery, the current study provides information that may improve the use of postoperative fever workups and thus decrease the overall cost of perioperative care.

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