David S. Warner, M.D., and Mark A. Warner, M.D., Editors

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Temperature Monitoring and Perioperative Thermoregulation

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Most clinically available thermometers accurately report the temperature of whatever tissue is being measured. The difficulty is that no reliably core-temperature-measuring sites are completely noninvasive and easy to use—especially in patients not undergoing general anesthesia. Nonetheless, temperature can be reliably measured in most patients. Body temperature should be measured in patients undergoing general anesthesia exceeding 30 min in duration and in patients undergoing major operations during neuraxial anesthesia. Core body temperature is normally tightly regulated. All general anesthetics produce a profound dose-dependent reduction in the core temperature, triggering cold defenses, including arteriovenous shunt vasoconstriction and shivering. Anesthetic-induced impairment of normal thermoregulatory control, with the resulting core-to-peripheral redistribution of body heat, is the primary cause of hypothermia in most patients. Neuraxial anesthesia also impairs thermoregulatory control, although to a lesser extent than does general anesthesia. Prolonged epidural analgesia is associated with hyperthermia whose cause remains unknown.

IN previous articles, I have reviewed heat balance in surgical patients,[1] complications associated with perioperative thermal perturbations,[2] and the etiology and treatments of postoperative shivering.[3] Heier and Caldwell[4] have reviewed the effects of hypothermia on the response to neuromuscular blocking drugs. Furthermore, an entire book is devoted to the emerging field of therapeutic hypothermia.[5] In this article, I will belatedly review temperature monitoring and the effects of general and regional anesthesia on thermoregulatory control.

Surgery typically involves exposure to a cold environment, administration of unwarmed intravenous fluids, and evaporation from within surgical incisions. However, these factors alone would not usually cause hypothermia; instead, thermoregulatory defenses would normally maintain core temperature in the face of comparable environmental stress. That hypothermia is typical in unwarmed surgical patients reflects a failure of effective thermoregulatory defenses. Understanding the effects of anesthetics on normal thermoregulatory control is thus the key to perioperative thermal perturbations because ineffective thermoregulation—much more than cold exposure—underlies most temperature changes observed in surgical patients.

I will first briefly review temperature monitoring and normal thermoregulation, and then discuss the effects of general and neuraxial anesthesia on temperature control.

Temperature Monitoring

Body temperature is not homogeneous: deep thoracic, abdominal, and central nervous system (*i.e.*, core) temperatures are usually 2° to 4°C warmer than the arms and legs—and much of the skin surface is cooler yet. Unlike core temperature, which is tightly regulated, skin temperature varies markedly as a function of environmental exposure; temperature of peripheral tissues (mostly the arms and legs) depends on current exposure, exposure history, core temperature, and thermoregulatory vasomotion. Core temperature, although by no means completely characterizing body heat content and distribution, is the best single indicator of thermal status in humans.

Core temperature monitoring (*e.g.*, tympanic membrane, pulmonary artery, distal esophagus, nasopharynx) is used to monitor intraoperative hypothermia, prevent overheating, and facilitate detection of malignant hyperthermia. Because these sites are not necessarily available or convenient, a variety of "near-core" sites are also used clinically. These include the mouth, axilla, bladder, rectum, and skin surface. Each has distinct limitations but can be used clinically in appropriate circumstances.

What level of accuracy is clinically necessary has yet to be established. But a good rule of thumb, one that has been used in many studies, is that the combined inaccuracy of a site–thermometer combination should not exceed 0.5°C. One basis for this choice is that 0.5°C is the smallest difference that has been shown to be associated with hypothermia-induced complications.[6]

Muscle or skin-surface temperatures may be used to evaluate vasomotion[7] and assure validity of peripheral neuromuscular monitoring.[4] Muscle temperatures are

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also used to determine peripheral compartment temperatures and regional distribution of body heat.[8–10] Both core and mean skin-surface temperature measurements are required to determine the thermoregulatory effects of different anesthetic drugs[11] and estimate mean body temperature (MBT).[12]

Thermometers

Mercury-in-glass thermometers are slow and cumbersome, and spilled mercury is a biohazard; they have thus all but disappeared from clinical use—although they remain useful for laboratory calibration of other systems. The most common electronic thermometers are thermistors and thermocouples. Thermistors are temperature-sensitive semiconductors, whereas thermocouples depend on the tiny current generated when dissimilar metals are joined. Both devices are sufficiently accurate for clinical use and inexpensive enough to be disposable. However, the signals from each are inherently nonlinear and thus need to be linearized by calibrated compensating units.

Infrared sensors are another type of thermometer that has become popular in the past decade. They work by evaluating infrared energy that is emitted by all surfaces above absolute zero degrees. They can consequently be used without actually touching the surface in question (which is useful for measuring the temperature of molten lava or metals, for example). These thermometers are accurate and relatively inexpensive. Clinical models can measure temperature of the skin surface to within a 10th of a degree or so. When infrared signals are actually obtained from the tympanic membrane, the result is core temperature.[13,14] However, nearly all available systems are intentionally too large to even fit more than a few millimeters into the aural canal and do not "see" anywhere near the tympanic membrane. As normally used, *i.e.*, directed into the aural canal[15] or near the temporal artery,[16] infrared systems are insufficiently accurate for clinical use (fig. 1). In light of their poor performance, it seems unfortunate that they have become so popular.

An interesting method of measuring core temperature from the surface of the skin is to use a system originally proposed by Fox *et al.*[17,18] and refined by Togawa *et al.*[19] The technique is to combine a heater with a thermal flux transducer (which is, effectively, two thermometers separated by a known thermal insulator). The heater is then servo-controlled until flux is zero. At this point, heat and skin temperature are, by definition, equal because there would otherwise be a flow of heat. However, the same logic suggests that there is no flow of heat from skin to deeper tissues; otherwise, heat would accumulate, which would violate the second law of thermodynamics. This logic is not quite accurate because it ignores blood-borne lateral convection of heat. But in practice, these thermometers accurately determine the

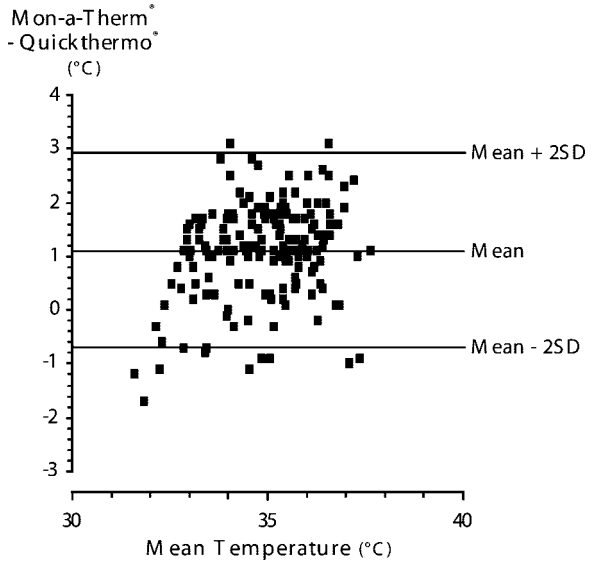

Fig. 1. The differences between the tympanic membrane thermocouple (Mon-a-therm, St. Louis, MO) and aural canal temperature measured by a Quickthermo infrared thermometer (Mie, Japan). The mean difference between core temperature and the infrared monitor was 1.1°C. Three other infrared monitors were evaluated in this study, but none proved sufficiently accurate for clinical use. From Imamura *et al.*[15]; used with permission from Wiley-Blackwell Publishing Ltd.

temperature of tissues to approximately a centimeter below the skin surface. In many parts of the body, notably the chest and forehead, a centimeter is sufficient to approximate core temperature (fig. 2).[20] Unfortunately, these otherwise excellent monitors are not currently available in Europe or the United States.

When Temperature Monitoring Is Required

Core temperature monitoring is appropriate during most general anesthetics both to facilitate detection of malignant hyperthermia and to quantify hyperthermia and hypothermia. Malignant hyperthermia is best de-

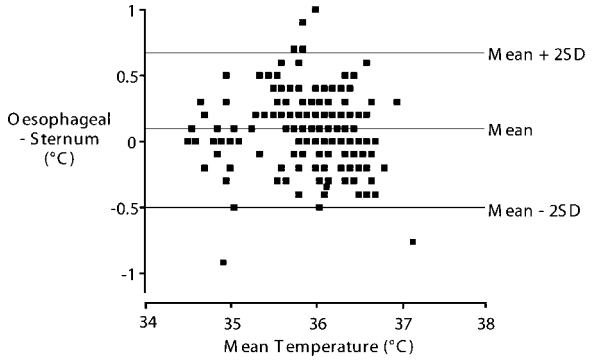

Fig. 2. Bland and Altman comparison of distal esophageal temperature and "deep sternal" temperatures. The *vertical axis* is the difference between esophageal and deep sternal temperatures. Mean temperature on the *horizontal axis* refers to the average between esophageal and deep sternal temperatures at each measurement time. The mean offset was 0.1°C, with an SD of 0.3°C. This accuracy is perfectly adequate for clinical use. From Matsukawa *et al.*[20]; used with permission.

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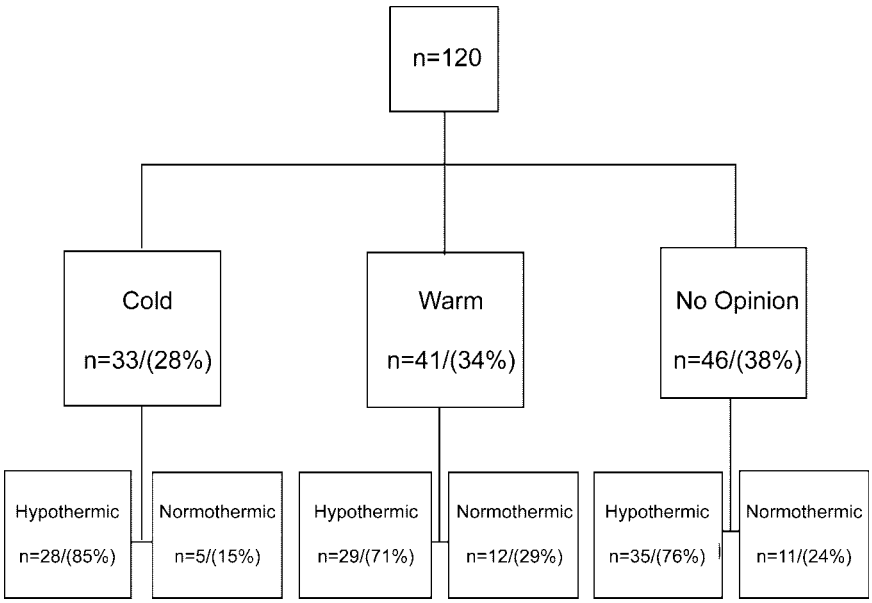

Fig. 3. All patients were divided by anesthesiologists' impression of thermal status. There was no difference in the number of hypothermic (< 36°C) and normothermic patients (P = 0.36) when divided by anesthesiologists' impression. Anesthesiologists were unable to reliably estimate their patients' thermal status. From Arkilic *et al.*[42]; used with permission. Copyright © 2000, Lippincott Williams & Wilkins.

tected by tachycardia and an increase in end-tidal partial pressure of carbon dioxide out of proportion to minute ventilation.[21] Although increasing core temperature is not the first sign of acute malignant hyperthermia, it certainly helps to confirm the diagnosis. More common than malignant hyperthermia is intraoperative hyperthermia having other etiologies, including excessive warming, infectious fever, blood in the fourth cerebral ventricle, and mismatched blood transfusions. Because hyperthermia has so many serious etiologies, any perioperative hyperthermia requires diagnostic attention.

By far the most common perioperative thermal disturbance is inadvertent hypothermia. Prospective, randomized trials have shown that even mild hypothermia causes numerous adverse outcomes in a variety of patient populations. Hypothermia-induced complications include morbid myocardial outcomes[22] secondary to sympathetic nervous system activation,[23] surgical wound infection,[24,25] coagulopathy,[6,26–33] increased allogeneic transfusions,[6,24,26,27,31,33–37] negative nitrogen balance,[38] delayed wound healing,[24] delayed postanesthetic recovery,[39] prolonged hospitalization,[24] shivering,[40] and patient discomfort.[41]

The major cause of hypothermia in most patients given general anesthesia is an internal core-to-peripheral redistribution of body heat that usually reduces core temperature by 0.5°–1.5°C in the first 30 min after induction of anesthesia. Hypothermia results from internal redistribution of heat and a variety of other factors whose importance in individual patients is hard to predict.[9] Core temperature perturbations during the first 30 min of anesthesia thus are difficult to interpret and measurements are not usually required. Body temperature should, however, be monitored in most patients undergoing general anesthesia exceeding 30 min in duration and in all patients whose surgery lasts longer than 1 h. Measuring body temperature (and maintaining normothermia) is now essentially the standard of care during prolonged general anesthesia, especially for large operations where the risk of hypothermia is substantial.

Hypothermia, resulting largely from core-to-peripheral redistribution of body heat,[8] is as common during epidural and spinal anesthesia as it is during general anesthesia, and can be nearly as severe.[42] Because neuraxial anesthesia impairs behavioral thermoregulatory responses (*i.e.*, patient sensation of cold),[43] patients and physicians are both frequently unaware that hypothermia has developed (fig. 3).[42] Core temperature should therefore be measured during regional anesthesia in patients likely to become hypothermic, including those undergoing body cavity surgery—although temperature monitoring during neuraxial anesthesia remains relatively uncommon.[44,45]

Monitoring Sites

The core thermal compartment is composed of highly perfused tissues whose temperature is uniform and high compared with the rest of the body. Temperature in this compartment can be evaluated in the pulmonary artery, distal esophagus, tympanic membrane, or nasopharynx.[46,47] Even during rapid thermal perturbations (*e.g.*, cardiopulmonary bypass), these temperature-monitoring sites remain reliable—although there may be transient real differences among them.

Temperature probes incorporated into esophageal stethoscopes must be positioned at the point of maximal heart sounds, or even more distally, to provide accurate readings.[48] Modern tympanic thermocouples are soft and pliable. There is thus little if any risk of perforating the membrane, although it is possible to push a bolus of wax onto the tympanic membrane. Inserting tympanic probes is somewhat more difficult than it sounds, espe-

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cially in conscious subjects, because the aural canal is several centimeters long and is not straight. The difficulty is that subjects and people inserting the probes often mistake the bend in the canal for the tympanic membrane and thus do not position the probes on the membrane itself. Once the probes are properly positioned, it is helpful to occlude the aural canal with cotton to prevent air currents from cooling the thermocouple. Nasopharyngeal probes should be inserted at least a few centimeters past the nares to obtain core temperature; nasopharyngeal temperatures are probably only accurate in patients who are not breathing through their nostrils.

Core temperature can be estimated with reasonable accuracy using oral, axillary, and bladder temperatures except during extreme thermal perturbations.[46,47] Each of these sites is subject to artifact so clinicians should use reasonable judgment in selecting a monitoring site (and type of thermometer) for a given patient. For example, oral temperatures can be inaccurate in patients who breathe through their mouths or have recently ingested hot or cold liquids. Axillary temperatures are reasonably accurate[49] but work best when the probe is positioned over the axillary artery and the arm is kept at the patient's side. Differences in technique may explain reported differences in accuracy.[50]

Skin-surface temperatures are considerably lower than core temperature[51]; forehead skin temperature, for example, is typically 2°C cooler than core. Perhaps surprisingly, even the intense vasodilation associated with sweating and the intense vasoconstriction associated with shivering only slightly alter the core-to-forehead temperature gradient (fig. 4).[52] Skin temperature is determined by the balance of heat provided by subcutaneous tissues and heat lost to the environment. Dissipation of heat from the skin surface, mostly by radiation and convection, depends on ambient temperature. While each type of heat loss is controlled by different equations, most of which are highly nonlinear, cutaneous heat loss is approximately linear over small ranges of ambient temperature. The 1°–2°C ambient temperature differences usually observed during surgery thus have little effect on the core-to-forehead temperature gradient (fig. 5).[52] Forehead skin temperature is thus a surprisingly accurate measure of core temperature so long as a +2°C compensation is included.

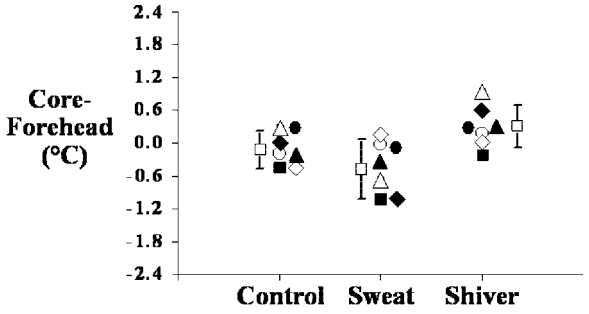

Fig. 4. Tympanic membrane (core) minus forehead skin-surface temperature difference during a thermoneutral control period was 0.1° ± 0.3°C. Skin temperature was augmented by 2°C for this calculation. This difference did not change significantly during vasodilation associated with sweating or vasoconstriction associated with shivering. Results are presented as mean ± SD. From Ikeda *et al.*[52]; used with permission. Copyright © 1997, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

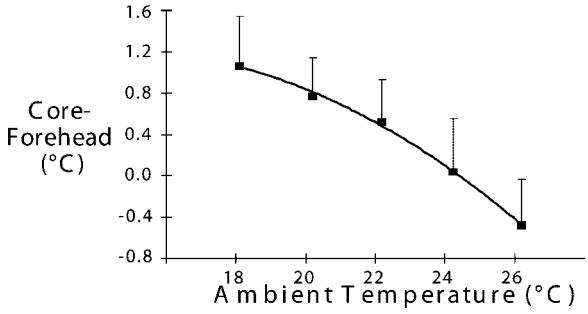

Fig. 5. The difference between tympanic membrane (core) and forehead skin-surface temperatures (ΔT) at ambient temperatures ($T_{ambient}$) between 18° and 26°C. Skin temperature was augmented by 2°C for this calculation. The data were fit to a second-order regression: $\Delta T = -0.58 + 0.29\ (T_{ambient}) - 0.01\ (T_{ambient})^2$, $r^2 = 0.999$. Each 1°C change in ambient temperature, starting near 22°C, thus altered skin temperature approximately 0.16°C. Results are presented as mean ± SD. Horizontal error bars (variation in ambient temperatures) are not displayed because they were smaller than the size of the markers. From Ikeda *et al.*[52]; used with permission. Copyright © 1997, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

A special case of skin-temperature monitoring is temporal artery thermometers. These are infrared skin-surface thermometers that record skin temperature at approximately 10 Hz and detect the highest temperature as the device is scanned across the forehead, including the region of the temporal artery. The theory is that the blood in the temporal artery is near core temperature and, therefore, that supervening skin temperature will also approximate core temperature. Although the theory is attractive, the devices are much too inaccurate for clinical use.[16,53]

A distinct limitation of skin temperatures is that they do not reliably confirm the clinical signs of malignant hyperthermia (tachycardia and hypercapnia) in swine (fig. 6)[54] and have not been evaluated for this purpose in humans. Rectal temperature also normally correlates well with core temperature[46,47] but does not increase appropriately during malignant hyperthermia crises[54] and under other documented situations, including heat stroke.[55,56] Consequently, rectal and skin-surface temperatures must be used with considerable caution.

The four core temperature monitoring sites (*i.e.*, tympanic membrane, nasopharynx, pulmonary artery, and esophagus) remain useful even during cardiopulmonary bypass. In contrast, rectal temperatures lag behind those measured in core sites. Consequently, rectal temperature is considered an "intermediate" temperature in deliberately cooled patients. During cardiac surgery, blad-

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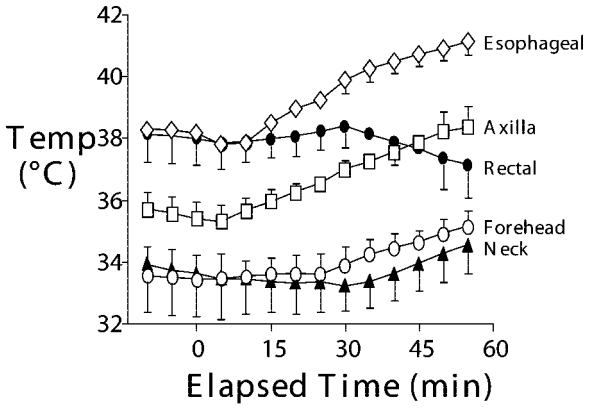

Fig. 6. Axillary and esophageal temperatures correlated well during acute malignant hyperthermia in swine, but forehead and neck skin temperatures did not. Rectal temperature also failed to promptly identify onset of malignant hyperthermia. Elapsed time zero indicates an end-tidal partial pressure of carbon dioxide of 70 mmHg. These data indicate that forehead and neck skin-surface temperatures will not adequately confirm other clinical signs of malignant hyperthermia. Valid core temperature monitoring sites include the distal esophagus, pulmonary artery, nasopharynx, and tympanic membrane. Except during cardiopulmonary bypass, body temperature also can be measured in the mouth, axilla, and bladder. Data are presented as mean ± SD. From Iaizzo *et al.*[54]; modified with permission. Copyright © 1996, Lippincott Williams & Wilkins.

der temperature is equal to rectal temperature (and therefore intermediate) when urine flow is low, but equal to pulmonary artery temperature (and thus core) when flow is high.[57] Because bladder temperature is strongly influenced by urine flow, it may be difficult to interpret in these patients. The adequacy of rewarming is best evaluated by considering both "core" and "intermediate" temperatures.

Mean Skin Temperature. Mean skin temperature is the area-weighted average temperature of the skin surface. Mean skin temperature, although less important than core temperature, is nonetheless important for at least three reasons: (1) Cutaneous heat loss is a function of mean skin temperature and ambient temperature; (2) central thermoregulatory control is determined by a combination of core and mean skin temperatures; and (3) the combination of core and mean skin temperatures can be used to estimate MBT and, therefore, body heat content.

Unsurprisingly, the accuracy of mean skin temperature measurements increases with the number of measurement sites. Therefore, 15 or more sites are usually used in thermoregulatory studies. For example, the following sites and regional weightings have been used in a hundred or more studies: head—6%, upper arms—9%, forearms—6%, hands—2.5%, fingers—2%, back—19%, chest—9.5%, abdomen—9.5%, medial thigh—6%, lateral thigh—6%, posterior thigh—7%, anterior calves—7.5%, posterior calves—4%, feet—4%, and toes—2%.[58] This large number of measurement sites results in accurate measurements even in the context of regional thermal manipulations (active heating or cooling) and when different amounts of insulation are used in various areas.

When thermal management (insulation or active heating or cooling) is uniformly distributed over the entire body, simpler formulas can be used without great loss of accuracy. A formula with only four sites was developed by Ramanathan[59] in 1964 and remains in common use: Mean skin temperature = 0.3 (chest + upper arm) + 0.2 (thigh + calf).

Mean Body Temperature. Changes in MBT over time can be determined by integrating the difference between metabolic heat production (oxygen consumption) and cutaneous heat loss (measured with thermal flux transducers). MBT can also be approximated as the mass-weighted sum of regional temperature distributions, which can be determined by integration of radial temperature distributions.[60] However, the technique is invasive and the computations tedious. Its use is consequently restricted to controlled studies in laboratories possessing the necessary equipment.[61]

In 1935, Burton[62] cleverly proposed that MBT could be calculated from a formula: $MBT = a \cdot T_{Core} + (1 - a) \cdot T_{Skin}$. The general form of the equation was based on the logic that core tissues are relatively homogeneous, whereas tissue temperature in the peripheral decreases parabolically from core temperature to skin temperature. The value of a, the coefficient describing the contribution of core temperature to MBT, was then estimated by simultaneously measuring the change in body heat content in a calorimeter, core temperature, and mean skin temperature. The resulting value of the coefficient α was 0.64, thus giving the formula: $MBT = 0.64 \cdot T_{Core} + 0.36 \cdot T_{Skin}$.

A similar approach has been used by others, including Hardy and DuBois,[63] who proposed a coefficient, a, of 0.7 for a neutral environment; Stolwijk and Hardy,[64] who proposed a coefficient of 0.7 for a hot environment; and Snellen,[65] who found the coefficient to be approximately 0.8 during muscular work in a hot environment. Subsequently, Colin *et al.*[66] showed in an elegant study that Burton's coefficient was correct for a neutral environment, but that the coefficient increased to 0.79 in an extremely warm environment.

Given all the assumptions about distribution of heat within the body that are necessary to estimate MBT from core and skin temperatures, it would be surprising if a simple formula based on core and mean skin temperatures were sufficient. But remarkably, it is. Even during cardiopulmonary bypass, the formula of Colin *et al.*[66] estimates MBT reasonably well (fig. 7).

Normal Thermoregulation

Normal Body Temperature Regulation

Body temperature is normally tightly regulated, more so even than blood pressure or heart rate. The control

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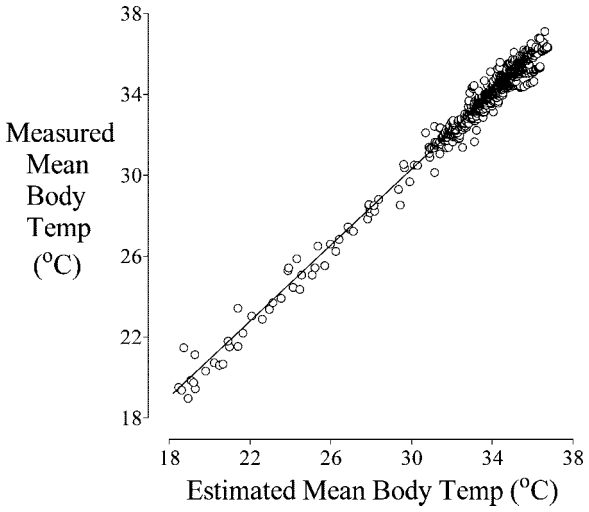

Fig. 7. Linear regression including 913 data pairs from 44 subjects who participated in four heat-balance studies. Mean body temperature (MBT) was estimated from core temperature and mean skin temperature and compared with directly measured values. There was a remarkably good relation between measured and estimated MBTs: $MBT_{estimated} = 0.94 \cdot MBT_{measured} + 2.15$, $r^2 = 0.98$. From Lenhardt and Sessler[12]; used with permission. Copyright © 2006, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

system is complex and involves parallel positive- and negative-feedback systems that are so widely distributed that nearly every part of the autonomic nervous system participates to some extent.

As early as 1912, physiologists recognized that the hypothalamus is the dominant thermoregulatory site in mammals because control was markedly compromised by injury or destruction of the hypothalamus. (The spinal cord serves this function in birds.) Interestingly, it took nearly another half century before the importance of thermal input from the skin was appreciated. It is now known that thermal signals from a variety of tissues and structures contribute thermal signals to the hypothalamus, and that there is considerable preprocessing of thermal information on the way from peripheral to central tissues.[67] Therefore, thermoregulation is based on multiple, redundant signals from nearly every type of tissue. The processing of thermoregulatory information occurs in three phases: afferent thermal sensing, central regulation, and efferent responses.

Afferent Input. Although all physiologic processes are, to some extent, temperature dependent, specific cells are markedly activated or inhibited by thermal perturbations. The assumption is that these cells are temperature sensors, and they are referred to as *warm-* or *cold-sensing cells*. Cold receptors, for example, increase their activity as tissue cools, whereas the reverse is true for heat sensors.

Because of its accessibility, cutaneous thermoreception is relatively well understood (see monograph by Hensel[68] for details). Human skin is phenomenally sensitive to temperature: An increase in forehead temperature of as little as 0.003°C can be detected. Apparent skin temperature and, more importantly, the ability to influence thermoregulatory responses is not uniform across the skin surface. The face is approximately five times as sensitive as other areas. Furthermore, sensitivity at differing sites depends somewhat on whether the skin is being warmed or cooled. The skin is far more sensitive to rapid thermal perturbations than to those occurring slowly.

Cold signals from the skin travel primarily *via* Aδ nerve fibers, whereas warm signals are transduced by unmyelinated C fibers.[69] Until recently, little was known about how Aδ and C fibers actually detect cutaneous temperature. However, it now seems that transient receptor potential (TRP) vanilloid (V) and menthol (M) receptors may be the fundamental temperature sensing elements in both skin and the dorsal root ganglia. These receptors, which have only been well characterized in recent years, are a family notable for having unusually high temperature sensitivity. Most change their activity by more than a factor of 10 over a 10°C range (Q10 > 10). TRPV1–4 receptors are heat activated, whereas TRPM8 and TRPA1 are activated by cold.[70,71]

Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. Recently, for example, an afferent somatosensory pathway *via* lateral parabrachial neurons has been shown to transmit signals directly to the preoptic thermoregulatory control center.[72] Consequently, the entire anterior cord must be destroyed to ablate thermoregulatory responses. The hypothalamus, other parts of the brain, the spinal cord, deep abdominal and thoracic tissues, and the skin surface each contribute very roughly 20% of the total thermal input to the central regulatory system.[73,74] Hence, although the hypothalamus is the dominant and most precise thermoregulatory controller, its temperature *per se* is not especially important.

Central Control. The simplest thermoregulatory model is the "set-point" system, in which all thermoregulatory responses are simultaneously turned on or off in response to hypothalamic temperature. This model is known to be an inadequate representation of the thermoregulatory system because (1) responses are determined by thermal input from nearly every portion of the body, (2) responses do not occur simultaneously or at similar temperatures, (3) the model does not incorporate a "null zone" in which no thermoregulatory responses occur, and (4) this model cannot explain thermal adaptation and a host of other observed phenomena.

The General Thermoregulatory Model. Consequently, I will review here a model that is somewhat more complicated, but considerably more useful. As with all models, this should be considered a framework from which to analyze thermoregulatory responses, not

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an actual mechanism by which the body produces those responses. In this model, thermal input from tissues throughout the body are integrated at a variety of centers (including the spinal cord and brain stem), but most importantly the hypothalamus. Individual responses are coordinated on the basis of weighted averages of the diverse inputs.

Temperature is regulated by central structures that compare integrated thermal inputs from the skin surface, neuraxis, and deep tissues with thresholds (triggering core temperatures) for each thermoregulatory response. Control is distributed in the sense that thermal input is integrated at various levels within the neuraxis, but the dominant controller in mammals is the hypothalamus, with autonomic control being centered in the anterior hypothalamus and behavioral control being centered in the posterior hypothalamus. This hierarchical arrangement presumably developed when the evolving thermoregulatory control system coopted previously existing mechanisms.[67] For example, muscles used for shivering were probably developed for posture and locomotion; similarly, thermoregulatory vasomotion is probably an offshoot of systems originally developed for hemodynamic control. It is likely that some thermoregulatory responses can be mounted by the spinal cord alone.[74] For example, animals and patients with high spinal-cord transections regulate temperature much worse than normal—but are not poikilothermic.

The slope of response intensity *versus* core temperature defines the gain of a thermoregulatory response. The maximum intensity of the response is defined as when response intensity no longer increases with further deviation in core temperature. Figure 8, for example, shows the normal sweating response as a function of distal esophageal core temperature during surface warming. There is only background insensible water loss from the skin without anesthesia until the threshold is reached at a core temperature of 36.5°C. The sweating rate then increases quickly as core temperature increases an additional 0.5°C (gain), but remains essentially constant with further hypothermia (maximum response intensity). Although the threshold increases as a function of isoflurane concentration, the gain and maximum intensity remain similar during anesthesia.[75]

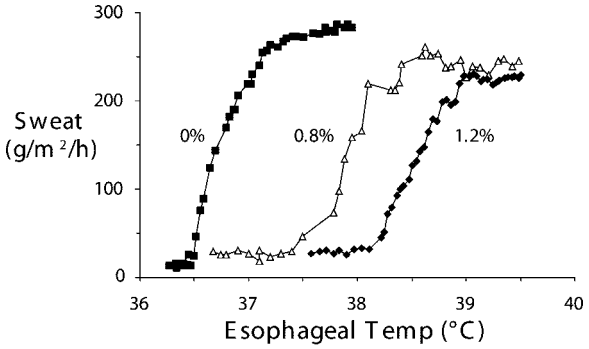

Fig. 8. The sweating rate in a typical male volunteer shows the threshold, gain, and maximum intensity during hyperthermia alone (0%) and at 0.8% and 1.2% end-tidal isoflurane concentration. The thresholds were markedly increased by anesthesia; in contrast, gains and maximum sweating rates were relatively well preserved. From Washington *et al.*[75]; used with permission.

Control of autonomic responses is approximately 80% determined by thermal input from core structures[76,77] and remains similar during anesthesia (fig. 9). In contrast, fully half of the input controlling behavioral responses are derived from the skin surface.[78]

Humans apparently measure temperature to great precision, but nonetheless tolerate an interthreshold range over which autonomic responses are not activated. This range of temperatures thus defines normal core temperature under given circumstances (*i.e.*, time of day, menstrual phase). Normal core temperatures in humans typically range from 36.5°C to 37.5°C; values less than 36°C or greater than 38°C usually indicate loss of control or a thermal environment so extreme that it overcomes thermoregulatory defenses.

Thermoregulatory modeling is thus complicated by interactions with other regulatory responses (*i.e.*, vascular volume control) and time-dependent effects. An area of continuing interest to physiologists is how humans handle environmental stress that would normally provoke opposing compensations. Heat stroke, for example, often results from dehydration in an excessively hot environment. Dehydration would normally activate water-retention mechanisms, whereas hyperthermia normally provokes sweating. Heat stroke, in fact, usually develops because the body cannot simultaneously compensate effectively for both perturbations.

Most thermoregulatory models (including the one described above) do not adequately account for the rate at which central and peripheral temperatures change. Consequently, they should be applied to vigorously dynamic situations with caution. Similarly, at least under some circumstances, thermoregulatory responses are not determined only by instantaneous thermal inputs, but instead reflect the recent history of thermal perturbations. The extent to which time- and temperature-dependent factors contribute to human thermoregulatory responses remains unclear.

Thresholds. How the body determines absolute threshold temperatures is incompletely understood, but seems to involve inhibitory postsynaptic potentials in hypothalamic neurons[79] that are modulated by norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, prostaglandin E_1, and neuropeptides. The thresholds vary daily by 0.5°–1°C in both sexes (circadian rhythm)[80] and by approximately 0.5°C with menstrual cycles in women.[81] Exercise, nutrition, infection, hypothyroidism and hyperthyroidism, drugs (including alcohol, sedatives, and nicotine), and cold and warm adaptation all alter threshold temperatures. But each of these

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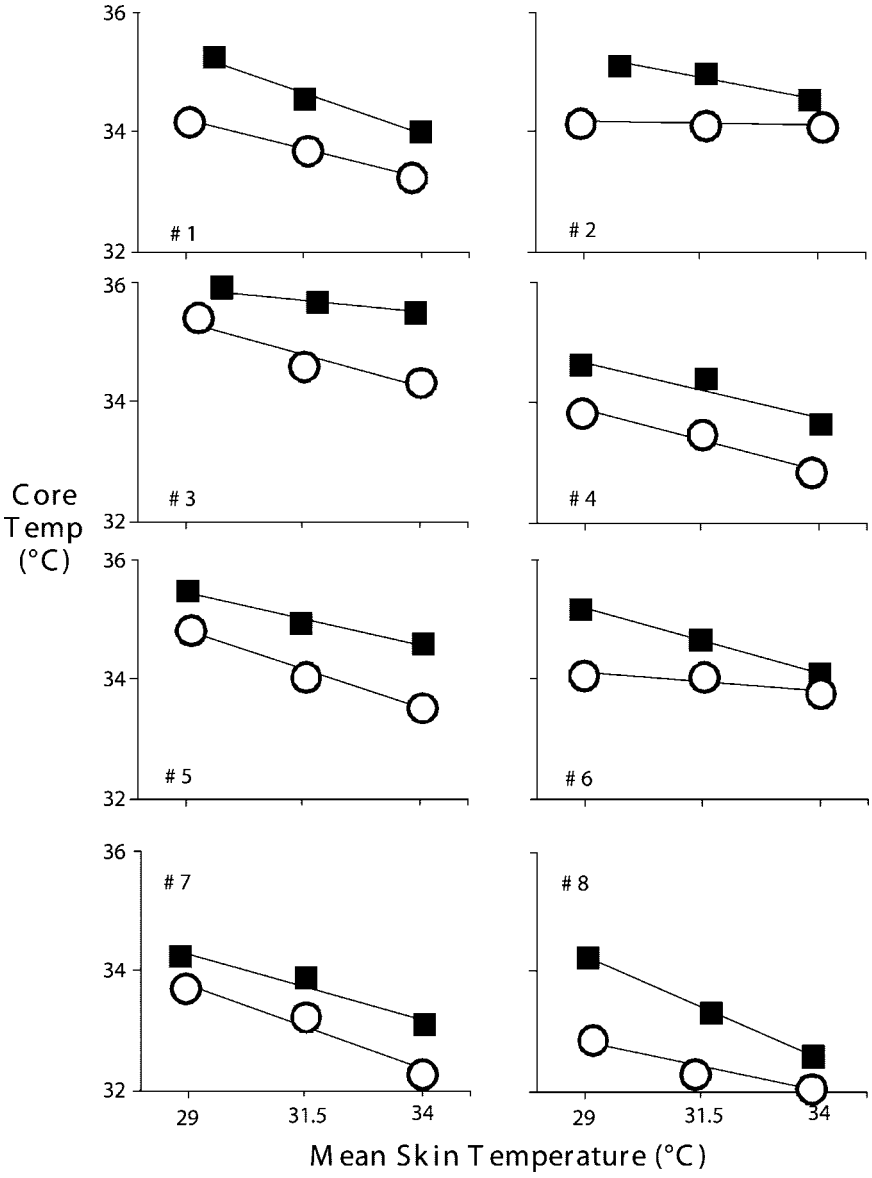

Fig. 9. Individual mean skin and core temperatures at the vasoconstriction (*squares*) and shivering (*circles*) thresholds in the eight volunteers. There was a linear relation between mean skin and core temperatures at the vasoconstriction and shivering thresholds in each volunteer (*lines*): r^2 = 0.98 ± 0.02 for vasoconstriction and 0.96 ± 0.04 for shivering. Relative contributions of skin and core temperatures varied from subject to subject, but on average skin temperature contributed 21 ± 8% to vasoconstriction and 18 ± 10% to shivering. From Lenhardt *et al.*[89]; used with permission. Copyright © 1999, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

effects is small compared with the profound impairment induced by general anesthesia.

The interthreshold range (core temperatures not triggering autonomic thermoregulatory responses) is bounded by the sweating threshold at its upper end and by the vasoconstriction threshold at the lower end. Within this range, temperatures are presumably sensed accurately but do not trigger regulatory responses. Teleologically, sacrificing a small degree of temperature regulation is prudent because energy and nutrients are not wasted aggressively combating small environmental changes.

The interthreshold range is usually only 0.2°–0.4°C in humans,[82] and that range defines normal body temperature. For unclear reasons, control is only half as tight at the circadian nadir near 3:00 AM (fig. 10).[80] Because energy cost and nutrients are conserved without excessive autonomic control or evaporative water loss within the interthreshold range, some animals, such as camels and desert rats, maintain a wide interthreshold range, allowing core temperature changes up to 10°C each day. However, this is very much the exception, and most mammals tightly control core temperature.

Both sweating and vasoconstriction thresholds are 0.3°–0.5°C higher in women than men, even during the follicular phase of the menstrual cycle (*i.e.*, first 10 days).[75] Differences are even greater during the luteal phase.[83] Central thermoregulatory control is apparently intact even in slightly premature infants[84] but is presumably immature in less-developed infants, such as those weighing less than a kilogram. The shivering threshold is well maintained in some elderly subjects well into their ninth decade, whereas others of that age regulate poorly; regulation, though, seems consistently normal in people aged younger than 80 yr.[85]

Efferent Responses. Some thermoregulatory responses are rarely, if ever, activated except by thermal

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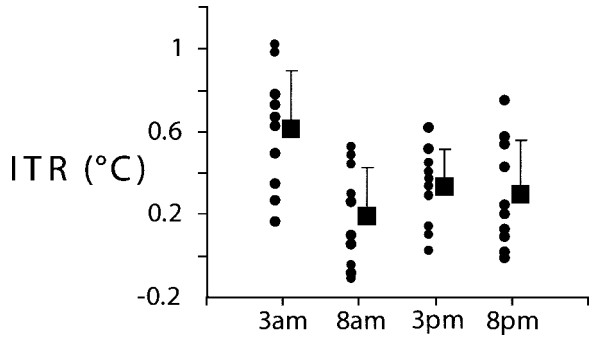

Fig. 10. The sweating-to-vasoconstriction interthreshold range (ITR) at each time of day. Data are presented as mean ± SD. Values at 3 AM differed significantly from those at other times. From Tayefeh *et al.*[80] (page 403, figure 2); copyright © 1998, reprinted with kind permission of Springer Science and Business Media.

perturbations. Such responses include sweating and brown fat metabolism. In other cases, the thermoregulatory system has coopted effector mechanisms developed for other purposes including shivering (postural and locomotive muscular activity) and vasomotion (blood pressure and osmotic control). Adaptation of preexisting systems for thermoregulatory control is consistent with the hierarchical thermoregulatory model proposed by Satinoff[67] and may explain why thermoregulatory control is so widely disbursed.

Thermal perturbations (defined by body temperature difference from a specific threshold) trigger effector responses that actually mediate appropriate increases in environmental heat loss or increases in metabolic heat production. Each response has its own threshold and gain. The control system is thus able to activate responses in an efficient order (*i.e.*, vasoconstriction before shivering, which is metabolically costly) and only to the extent actually necessary to maintain core temperature.

Behavioral Regulation. Behavioral regulation (intentional manipulation of heat exchange with the environment) is the most powerful thermoregulatory effector. It is such modification that allows humans to live in the warmest and coldest climates on Earth. Animals also use behavioral modification to alter heat balance with the environment. Behavioral regulation is most dramatic in reptiles and amphibians. These animals, often referred to as "cold-blooded," actually regulate their temperatures remarkably well and even develop behavioral "fever."[86] Given access to a reasonable range of environmental temperatures, they will position themselves to maintain a central temperature within a few degrees of "normal." Interestingly, the temperatures maintained as optimal by most reptiles is similar to that in mammals, near 37°C. Similarly, fish provided with a thermal gradient will position themselves to maintain a nearly constant central temperature.[87] One investigator was even able to train a goldfish to maintain his water (and therefore body) temperature nearly constant by pushing a button.[88] Even bacteria, given an opportunity, will position themselves to maintain optimal temperature.

Aggressive behavioral modification of environmental heat loss is not necessary in mammals exposed to reasonable environments. This has the evolutionary advantage of maintaining a nearly constant central temperature (presumably necessary for optimal enzyme function) without requiring behavioral modifications that might compromise survival. Nonetheless, when autonomic thermoregulatory responses are insufficient for maintaining central temperature, behavioral responses become critical for survival. Behavioral adaptations take many forms but most commonly involve simple maneuvers such as moving from direct sun into shade, dressing more warmly, or altering ambient temperature using a heating/air conditioning system. Behavioral responses require a conscious perception of body temperature. Intriguingly, humans seem to sense changes in central temperature poorly; in contrast, minute changes in skin-surface temperature are easily perceived. Therefore, behavioral thermoregulation is approximately half mediated by skin temperature,[78] whereas mean skin temperature contributes only 10–20% to the control of autonomic thermoregulatory defenses.[76,89]

Vasomotion. Most metabolic heat is lost from the skin surface and cutaneous vasoconstriction, the most consistently used autonomic effector mechanism, reduces this loss. Total digital skin blood flow is divided into nutritional (mostly capillary) and thermoregulatory (mostly arteriovenous shunt) components.[90] Shunts are typically 100 μm in diameter, which means that one shunt can convey 10,000-fold as much blood as a comparable length of capillary 10 μm in diameter. Arteriovenous shunt flow tends to be "on" or "off," which is simply a way of saying that the gain of this response is high. Roughly 10% of cardiac output traverses arteriovenous shunts; consequently, shunt vasoconstriction increases mean arterial pressure approximately 15 mmHg.[91]

Arteriovenous shunts are located only in acral regions (fingers, toes, nose, *etc.*). These specialized thermoregulatory vessels are under α-adrenergic control and are constricted by norepinephrine released from sympathetic nerves. Circulating factors seem to have little direct influence on arteriovenous shunts, although hormones such as angiotensin are known to facilitate the response to a given sympathetic stimulus. Most blood vessels constrict in response to local hypothermia, but arteriovenous shunts are relatively resistant to regional temperature perturbations and seem to be almost exclusively controlled by central thermoregulatory status. In a thermoneutral environment (*e.g.*, body temperature within the interthreshold range) or in a denervated extremity, arteriovenous shunts are fully dilated. However, at typical ambient temperatures, tonic sympathetic stimulation maintains minimal shunt flow.

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Nonshivering Thermogenesis. Nonshivering thermogenesis is defined as an increase in metabolic heat production not associated with muscular activity. This increase occurs largely in specialized fat called *brown adipose tissue*, located largely in the intrascapular and perirenal areas. Brown fat has a dark hue because it is loaded with mitochondria. When stimulated, this tissue has by far the highest metabolic rate of any organ (up to 0.5 W/g). Ordinarily, mitochondrial metabolism produces a proton that is secreted outside the sarcoplasmic reticulum. The proton gradient across this membrane subsequently activates the sodium–potassium adenosine triphosphatase, producing adenosine triphosphate from adenosine diphosphate. When stimulated by norepinephrine released from sympathetic nerves, mitochondrial respiration in brown adenosine triphosphatase tissue proceeds normally. However, production of adenosine triphosphate is prevented by an "uncoupling protein," which allows protons to reenter the sarcoplasmic reticulum without driving the sodium–potassium adenosine triphosphatase.[92]

Nonshivering thermogenesis is the primary defense against cold in small mammalian species such as mice and rats, and can easily double or triple metabolic heat production (measured as whole-body oxygen consumption) without producing mechanical work. Nonshivering thermogenesis also doubles heat production in infants.[93] The intensity of nonshivering thermogenesis is a linear function of the difference between MBT and its threshold.

But despite its importance in small animals and human infants, nonshivering thermogenesis is relatively unimportant or nonexistent in species having a relatively large body size (*i.e.*, $>$ 50 kg). In adult humans, nonshivering thermogenesis is poorly developed[94] and contributes little to thermal balance in adult humans.

Shivering. Sustained shivering augments metabolic heat production 50–100% in adults. This increase is small compared with that produced by exercise (which can, at least briefly, increase metabolism fivefold) and is thus surprisingly ineffective. Shivering is manifested as an irregular tremor that on electromyographic analysis consists of randomly overlapping myofibril depolarization spikes. Superimposed on this rapid and apparently disorganized local activity is a 4- to 10-cycles/min waxing-and-waning activity. Notably, this slow amplitude modulation is synchronous and occurs simultaneously in all muscles throughout the body.[95] Shivering does not occur in newborn infants and probably is not fully effective until children are several years old. Because the shivering threshold is a full degree less than the vasoconstriction threshold,[82] shivering seems to be a "last resort" response to extreme cold.

Sweating. Sweating is mediated by postganglionic, cholinergic nerves.[96] It thus is an active process that is prevented by nerve block or atropine administration.[97] Even untrained individuals can sweat up to 1 l/h, and athletes can sweat at twice that rate. Sweating is the only mechanism by which the body can dissipate heat in an environment exceeding core temperature. Fortunately, the process is remarkably effective: each gram of evaporated sweat dissipates 0.58 kcal. In a dry, convective environment, individuals can thus easily dissipate many times their basal metabolic rate, which is roughly a kcal $\cdot$ kg^{-1} $\cdot$ h^{-1}. Of course sweat that drips off the skin without evaporating contributes nothing to heat balance, but it does promote dehydration.

During exercise, muscle blood flow increases enormously and blood pressure can only be maintained by vasoconstriction in other vascular beds. Furthermore, exercise produces considerable heat which in most environments must be dissipated by increased capillary blood flow and sweating (1 l/h or more). Thermoregulatory compensations thus compete with the needs of muscle for increased blood flow. Consequently, it is unsurprising that maximum capillary blood flow and sweating rate are impaired by insufficient vascular volume and cardiovascular compromise. In light of the huge cardiovascular stresses imposed by exercise and the thermoregulatory compensation for the attendant increase in metabolic heat production, it is remarkable that humans can perform vigorously in a warm environment and maintain a reasonable blood pressure.

In contrast to shunt flow, capillary blood flow is minimal both at typical ambient temperatures and at thermoneutral temperatures. During heat stress, active dilation of precapillary arterials increases capillary blood flow enormously. This dilation certainly involves withdrawal of tonic sympathetic stimulation but also likely involves release of a yet-to-be-identified factor from sweat glands; the mediator may be nitric oxide or neuropeptide Y.[98] Because active vasodilation requires intact sweat gland function, it also is largely inhibited by nerve block. During extreme heat stress, blood flow through the top millimeter of skin can reach 7.5 l/min—equaling the entire resting cardiac output.[99] The threshold for active vasodilation usually is similar to the sweating threshold, but maximum cutaneous vasodilation usually is delayed until sweating intensity is at its maximum.

Response Activation Strategy. All potential thermoregulatory responses are ideally available and used in a specific order depending on their respective thresholds and response gains. However, one or more effectors may be disabled by circumstances. For example, social convention may restrict voluntary movement or the ability to seek a warmer or cooler environment. Or a muscle relaxant may prevent shivering or a vasodilator may restrict vasoconstriction. In such circumstances, remaining effectors compensate to the limit of their abilities. The result is that core temperature is usually nonetheless maintained, although the range of tolerated environments decreases.

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Hyperthermia

Hyperthermia is a generic term simply indicating a core body temperature exceeding normal values. In contrast, fever is a regulated increase in the core temperature targeted by the thermoregulatory system. Hyperthermia can result from a variety of causes and, unlike perioperative hypothermia, usually requires diagnosis and often intervention.

Passive Hyperthermia and Excessive Heat Production. Passive intraoperative hyperthermia results from excessive patient heating and is most common in infants and children. Perioperative hyperthermia was common in the tropics, before air conditioning became routine, and was aggravated by the frequent use of atropine.[100] Passive hyperthermia, by definition, does not result from thermoregulatory intervention. Consequently, it can easily be treated by discontinuing active warming and removing excessive insulation.

The increase in body temperature during malignant hyperthermia results from an enormous increase in metabolic heat produced by both internal organs and skeletal muscles. Central thermoregulation presumably remains intact during acute crises, but efferent heat loss mechanisms may be compromised by intense peripheral vasoconstriction resulting from circulating catecholamine concentrations 20 times normal.[101]

Fever. Body temperature is minimally influenced by circulating factors such as thyroid hormones; instead, it is normally maintained by neuronal systems. In contrast, fever is mediated by endogenous pyrogens which increase the thermoregulatory target temperature ("set point"). Endogenous pyrogens include interleukin 1, tumor necrosis factor, interferon α, endothelin 1, and macrophage inflammatory protein 1.[102,103] There is increasing evidence that vagal afferents mediate between systemic pyrogens and the hypothalamus,[104] although several systems probably contribute.[105] Most endogenous pyrogens have peripheral actions (*e.g.*, immune system activation) in addition to their central generating capabilities. The relative contributions of fever *per se* and the systemic action of endogenous pyrogens remain unclear; however, it seems that fever itself is an important immune defense.[106]

Fever is relatively rare during general anesthesia, considering how many patients presumably experience febrile stimuli, including surgical tissue injury. The reason intraoperative fever is rare is that volatile anesthetics *per se* inhibit expression of fever,[107] as do opioids.[108,109] Infection is by far the most common cause of fever. Such fevers may reflect preexisting infection or result, for example, from urologic manipulations. However, perioperative fever also occurs in response to mismatched blood transfusions, blood in the fourth cerebral ventricle, drug toxicity, and allergic reactions.[110,111] Some degree of fever is also typical after surgery, and presumably results from the inflammatory response to surgery.[112] There is no evidence to support the common attribution of postoperative fever to atelectasis. Instead, the causes of fever are sufficiently diverse—and potentially serious—that physicians caring for febrile patients should consider potential etiologies.

Treatment of hyperthermia depends on the etiology; the critical distinction is between actively maintained fever and hyperthermia that results from excessive heating, inadequate dissipation of metabolic heat, or excessive heat production. A simple way to distinguish the etiologies is that patients with fever and increasing core temperature will have constricted, cold fingertips, whereas those with other types of hyperthermia will be vasodilated and have warm fingertips. It is always appropriate to treat underlying causes, but nonfebrile hyperthermia will also improve with cooling.

The first- and second-line treatments for fever are amelioration of the underlying cause and administration of antipyretic medications.[113] The first treatment strategy often fails because the etiology of fever remains either unknown or unresponsive. The second strategy also often fails or is only partially effective, perhaps because some fever is mediated by mechanisms that bypass conventional antipyretics.[102] It is in these patients that third-line treatment is most likely to be implemented: active cooling. Active cooling of febrile patients is a natural response. However, it often fails to reduce core temperature—while simultaneously worsening the situation by triggering thermoregulatory defenses, including intense discomfort, shivering, and autonomic nervous system activation.[114,115]

Active cooling should thus be used with considerable caution in febrile patients, with great attention to the metabolic and vasomotor consequences—to say nothing of the resulting thermal discomfort. Systems that directly cool the core[116–118] provoke less thermoregulatory stress than surface-based systems,[115] especially when intense core cooling is combined with gentle surface warming. A general clinical guideline is that cooling which maintains or decreases oxygen consumption is likely to be helpful,[119] whereas an increasing metabolic rate indicates a potentially harmful activation of thermoregulatory responses.

Thermoregulation during General Anesthesia

Anesthetized patients cannot activate behavioral responses, leaving them to rely on autonomic defenses and external thermal management. All general anesthetics so far tested markedly impair normal autonomic thermoregulatory control. Anesthetic-induced impairment has a specific form: warm-response thresholds are elevated slightly, if at all, whereas cold-response thresholds are markedly reduced. Consequently, the interthreshold range increases 10-fold to approximately 2°–4°C.[109,120–123]

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The gain and maximum intensity of some responses remain normal,[75] whereas general anesthesia reduces others.[124,125]

Response Thresholds

Propofol,[120] alfentanil,[109] dexmedetomidine,[121] isoflurane,[123] and desflurane[122] all increase the sweating threshold only slightly, if at all. Warm defenses are thus well preserved even during general anesthesia. A consequence is that inadvertent hyperthermia during forced-air warming is relatively rare because patients are usually able to dissipate excess heat into their dry, convective microenvironment. They are less protected against hyperthermia with the newer circulating-water garments that not only transfer more heat,[61] but are impervious to moisture, thus preventing evaporative heat loss.

Propofol,[120] alfentanil,[109] and dexmedetomidine[121] produce a marked and linear decrease in the vasoconstriction and shivering thresholds. In contrast, isoflurane[123] and desflurane[122] decrease the cold-response thresholds nonlinearly. Consequently, the volatile anesthetics inhibit vasoconstriction and shivering less than propofol at low concentrations, but more than propofol at typical anesthetic doses.

Interestingly, the normal approximately 1°C difference between the vasoconstriction and shivering thresholds is maintained even when patients are given sedatives or general anesthesia. That the relation between these two thresholds is so precisely maintained under a large variety of circumstances suggests that both major autonomic cold defenses are similarly controlled, perhaps by an identical central regulator. The only exceptions to comparable control identified to date are nefopam[126] and meperidine, which reduces the shivering threshold twice as much as the vasoconstriction threshold[127]—explaining the drug's potent antishivering action.[128,129]

The dose-dependent response thresholds for four anesthetic drugs are shown in figure 11. These responses are characteristic of the drugs and drug combinations that have so far been tested. The combination of increased sweating thresholds and reduced vasoconstriction thresholds increases the interthreshold range 10-fold, from its normal value near 0.2°–0.4°C to approximately 2°–4°C. Temperatures within this range do not trigger thermoregulatory defenses; by definition, patients are thus poikilothermic within this temperature range.

Halothane,[130] enflurane,[131] and the combination of nitrous oxide and fentanyl[132] decrease the vasoconstriction threshold 2°–4°C from its normal value near 37°C. The effects of these drugs on sweating or shivering remain unknown, but experience with other drugs suggests that they are unlikely to have much effect on sweating but have a profound effect on shivering. Clonidine synchronously decreases cold-response thresholds,[133] while slightly increasing the sweating threshold.[134] Nitrous oxide decreases the vasoconstriction[135] and shivering[136] thresholds less than equipotent concentrations of volatile anesthetics.

Midazolam, in typical clinical doses, minimally influences thermoregulatory control.[137,138] Painful stimulation slightly increases vasoconstriction thresholds[131] just as pain has an antianesthetic effect[139] and regional anesthesia has a proanesthetic action.[140] Consequently, thresholds will be somewhat lower when surgical pain is prevented by simultaneous local or regional anesthesia. Both amino acid[141] and fructose[142] infusions increase the vasoconstriction threshold by approximately 0.5°C.

The effects of vascular volume on thermoregulatory vasoconstriction have not been evaluated during anesthesia. But positive end-expiratory pressure increases the vasoconstriction threshold, whereas increasing cen-

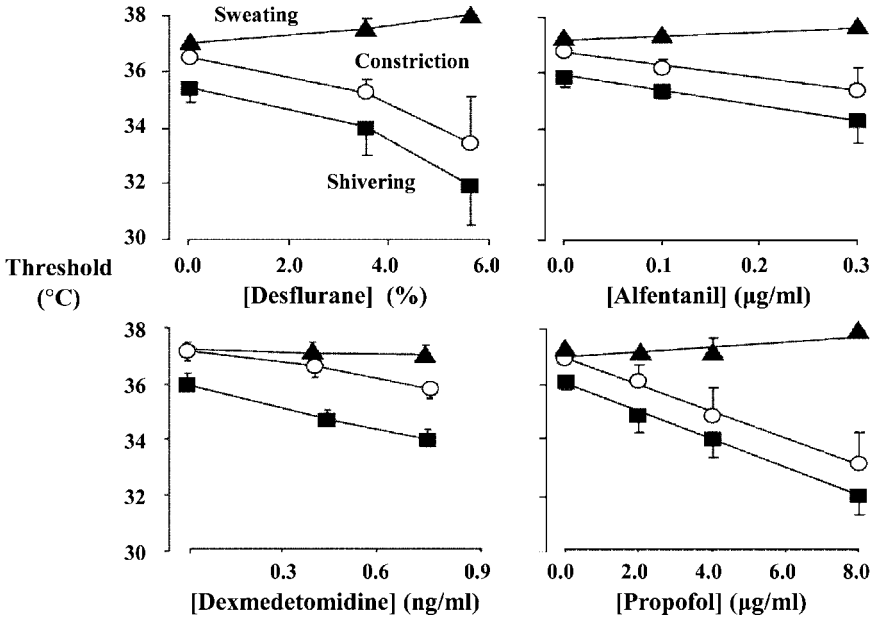

Fig. 11. The major autonomic thermoregulatory response thresholds in volunteers given desflurane, alfentanil, dexmedetomidine, or propofol. All of the anesthetics slightly increase the sweating threshold (triggering core temperature) while markedly and synchronously decreasing the vasoconstriction and shivering thresholds. SD bars smaller than the data markers have been deleted. Used with permission.[109,120–122] Copyright © 1995, 1997, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

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tral blood volume by leg raising reduces the threshold.[143] Baroreceptor unloading augments the peripheral vasoconstrictor and catecholamine response to core hypothermia while simultaneously reducing thermogenesis—which consequently aggravates hypothermia in the upright position. Upright posture attenuates the thermogenic response to core hypothermia but augments peripheral vasoconstriction. This divergent result suggests that input from the baroreceptor modifies the individual thermoregulatory efferent pathway at a site distal to the common thermoregulatory center or neural pathway.[144]

Gain and Maximum Response Intensity

Both the gain and maximum intensity of sweating remain normal during isoflurane (fig. 8)[75] and enflurane anesthesia.[145] However, the gain of arteriovenous shunt vasoconstriction is reduced threefold during desflurane anesthesia (fig. 12),[124] even though the maximum vasoconstriction intensity remains normal.[146] Volatile anesthetics thus not only markedly decrease the vasoconstriction threshold,[122,123] but once triggered, three times as much additional hypothermia as normal is required to reach maximum vasoconstriction. Fortunately, maximum intensity is finally reached and, once reached, is effective, usually preventing further core hypothermia.[10]

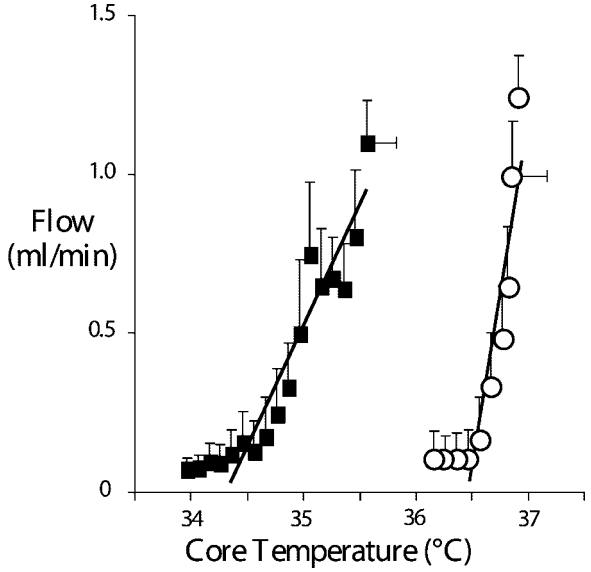

Fig. 12. Finger blood flow without (*open circles*) and with (*filled squares*) desflurane administration. Values were computed relative to the thresholds (finger flow = 1.0 ml/min) in each subject. Flows of exactly 1.0 ml/min are not shown because flows in each individual were averaged over 0.1° or 0.05°C increments; each *data point* thus includes both higher and lower flows. The *horizontal SD bars* indicate variability in the thresholds among the volunteers; although error bars are shown only at a flow near 1.0 ml/min, the same temperature variability applies to each data point. The slopes of the flow–*versus*–core temperature relations (1.0 to approximately 0.15 ml/min) were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced by a factor of 3, from 2.4 to 0.8 ml · min^{-1} · °C^{-1} ($P < 0.01$). From Kurz *et al.*[124]; used with permission. Copyright © 1995, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

Shivering is rare with surgical doses of general anesthesia, which is consistent with its threshold being roughly 1°C less than the vasoconstriction threshold.[109,120–123] The reason is that vasoconstriction is effective, constraining metabolic heat to the core thermal compartment, thus usually preventing additional hypothermia.[10] Consequently, it is rare even for unwarmed patients to become cold enough to induce shivering. Nonetheless, sufficient active cooling can induce shivering.

Gain and maximum shivering intensity remain normal during both meperidine and alfentanil administration.[147] Gain also remains nearly intact during nitrous oxide administration, although maximum intensity is reduced.[148] Isoflurane changes the macroscopic pattern of shivering to such an extent that it is no longer possible to easily determine gain. The drug does, however, reduce maximum shivering intensity.[125]

To sum up, sweating is the thermoregulatory defense that is best preserved during anesthesia. Not only is the threshold only slightly increased, but also the gain and maximum intensity are well preserved. In contrast, the thresholds for vasoconstriction and shivering are markedly reduced, and furthermore, these responses are less effective than normal even after being activated.

It would be intuitive to conclude that surgical patients become hypothermic because they are minimally covered, exposed to a cold environment, and washed with cold fluids that are allowed to evaporate, because surgery *per se* increases heat loss from within incisions, and because general anesthesia reduces metabolic rate. However, even the combination of all these factors would rarely produce hypothermia in subjects with intact thermoregulatory defenses. Anesthetic-induced thermoregulatory impairment is thus by far the most important cause of perioperative hypothermia.

Responses in Infants and the Elderly

As we have seen, thermoregulatory control is profoundly impaired by most any type of general anesthesia in adults, resulting in a large interthreshold range (*i.e.*, 2°–4°C) over which core temperature perturbations fail to trigger regulatory defenses. Thermoregulatory control is equally bad in anesthetized infants and children but does not seem to be worse. For example, thermoregulatory vasoconstriction is comparably impaired in infants, children, and adults given isoflurane[149] or halothane[150] (fig. 13). In contrast, the vasoconstriction threshold is approximately 1°C less in patients aged 60–80 yr than in those aged between 30 and 50 yr (fig. 14).[151,152] Infants are nonetheless at special risk of hypothermia because their large surface area–to–mass ratio increases the relative difference between heat loss and heat production.

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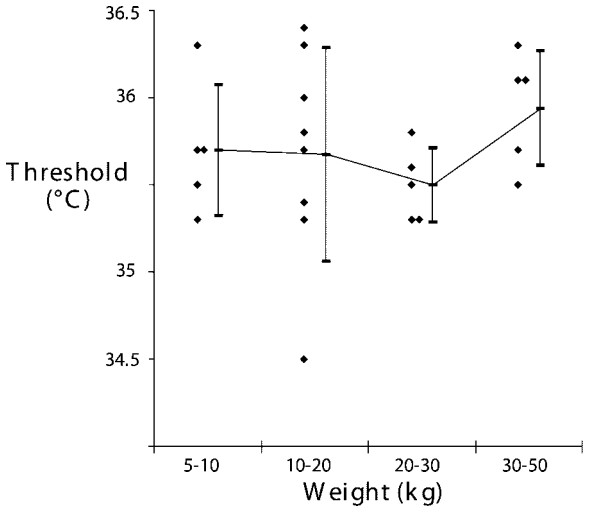

Fig. 13. The core thermoregulatory threshold in 23 healthy children and infants undergoing abdominal surgery with halothane anesthesia. Differences among the groups are not statistically significant. Results are presented as mean ± SD. From Bissonnette and Sessler[150]; used with permission. Copyright © 1992, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

Nonshivering thermogenesis does not occur in anesthetized adults,[153] which is hardly surprising because this response is not particularly important in unanesthetized adults.[94] In contrast to adult humans, nonshivering thermogenesis is an important thermoregulatory response in animals and human infants. However, nonshivering thermogenesis in animals is inhibited by volatile anesthetics,[154] and it does not increase the metabolic rate in infants anesthetized with propofol.[155] It thus seems that nonshivering thermogenesis is relatively unimportant in perioperative patients and certainly has a small effect compared with the approximately 30% reduction in metabolic rate associated with general anesthesia.

Thermoregulation during Neuraxial Anesthesia

Central thermoregulatory control is slightly impaired by neuraxial anesthesia, but this is combined with reduced gain and maximum response intensity of shivering. Autonomic impairment is compounded by an impairment of behavioral regulation so that patients do not recognize that they are hypothermic. And finally, core temperature is not usually monitored during neuraxial anesthesia.

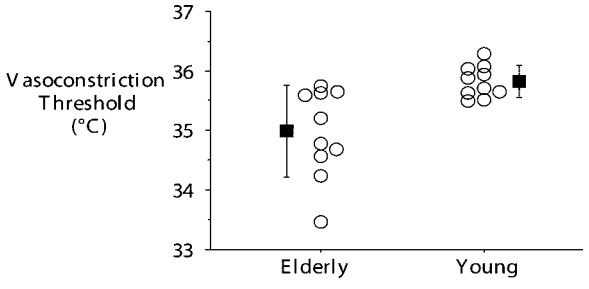

Fig. 14. The vasoconstriction threshold during light sevoflurane anesthesia was significantly less in elderly (35.8° ± 0.3°C, n = 10) than in younger patients (35.0° ± 0.5°C, n = 10) ($P < 0.01$). *Open circles* indicate the vasoconstriction threshold in each patient; *filled squares* indicate the mean and SD in each group. From Ozaki *et al.*[152]; used with permission. Copyright © 1997. Lippincott Williams & Wilkins.

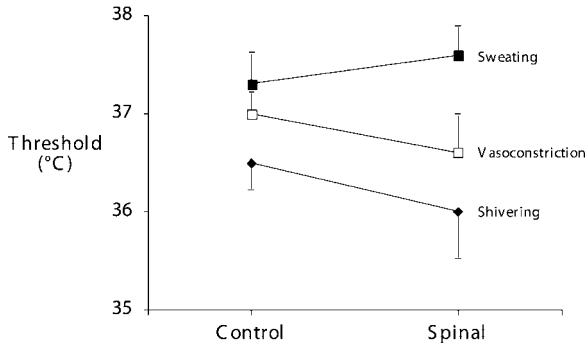

Fig. 15. Spinal anesthesia increased the sweating threshold but reduced the thresholds for vasoconstriction and shivering. Consequently, the interthreshold range increased substantially. The vasoconstriction-to-shivering range, however, remained normal during spinal anesthesia. Results are presented as mean ± SD. From Kurz *et al.*[157]; used with permission. Copyright © 1993. Lippincott Williams & Wilkins.

The result is that patients undergoing neuraxial anesthesia typically become hypothermic and do not sense the hypothermia. In addition, the anesthesiologist does not detect the hypothermia. This is problematic because there is little reason to believe that patients having neuraxial anesthesia are protected from the well-established complications of hypothermia.

Response Thresholds

Epidural[43,156] and spinal[156,157] anesthesia each decrease the thresholds triggering vasoconstriction and shivering (above the level of the block) approximately 0.6°C (fig. 15). Although the magnitude is less, the pattern of impairment is thus similar to that observed with general anesthetics and opioids, suggesting an alteration in central rather than peripheral control. The mechanism by which peripheral administration of local anesthesia impairs centrally mediated thermoregulation remains unknown but is proportional to the number of spinal segments blocked (fig. 16).[158]

Reduced thresholds during neuraxial anesthesia do not result from recirculation of neuraxially administered local anesthetic because impairment is similar during epidural and spinal anesthesia,[43,156,157] although the amount and location of administered local anesthetic differs substantially. Furthermore, lidocaine administered intravenously in doses producing plasma concentrations similar to those occurring during epidural anesthesia has no thermoregulatory effect.[159] Finally, neuraxial administration of 2-chloroprocaine, a local anesthetic that has a plasma half-life of only a few minutes, also impairs thermoregulatory control.[160]

Because neuraxial anesthesia prevents vasoconstriction and shivering in blocked regions, it is unsurprising

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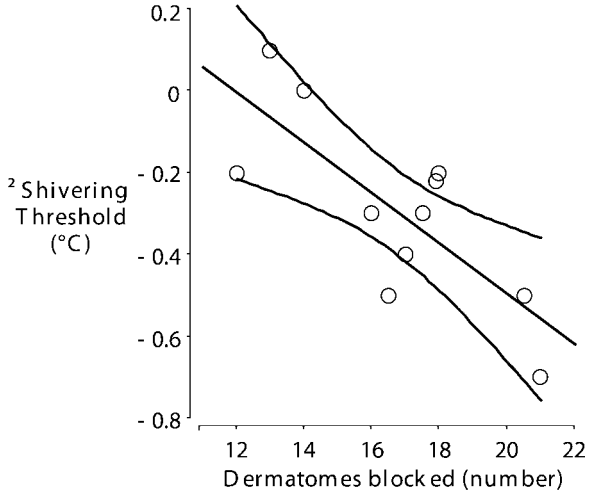

Fig. 16. The number of dermatomes blocked (sacral segments = 5; lumbar segments = 5; thoracic segments = 12) *versus* reduction in the shivering threshold (difference between the control shivering threshold and spinal shivering threshold). The shivering threshold was reduced more by extensive spinal blocks than by less extensive ones (Δ threshold = 0.74–0.06 (dermatomes blocked); r^2 = 0.58, P < 0.006). The *curved lines* indicate the 95% confidence intervals for the slope. From Leslie and Sessler[158]; used with permission. Copyright © 1996, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

that epidural anesthesia decreases the maximum intensity of shivering. However, epidural anesthesia also reduces the gain of shivering, which suggests that the regulatory system is unable to compensate for lower

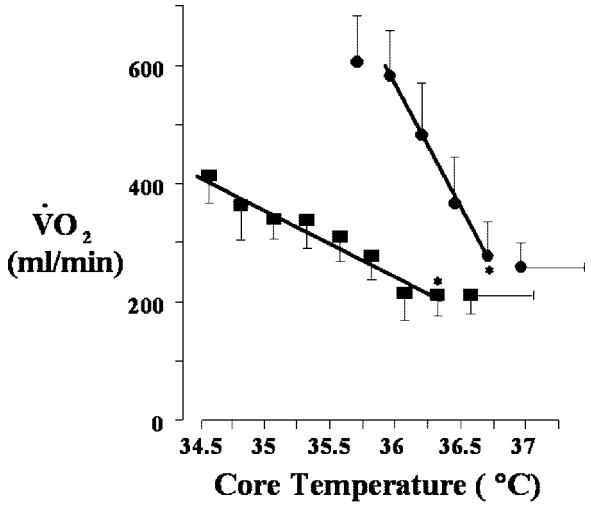

Fig. 17. Systemic oxygen consumption (Vo_2) without (*circles*) and with (*squares*) epidural anesthesia. * Indicates the threshold under each condition. The *horizontal SD bars* indicate variability in the thresholds among the volunteers; although errors bars are shown only once in each series, the same temperature variability applies to each data point. The slopes of the oxygen consumption *versus* core temperature relations (*solid lines*) were determined using linear regression. These slopes defined the gain of shivering with and without epidural anesthesia. Gain was reduced 3.7-fold, from −412 ml · min^{-1} · °C^{-1} (r^2 = 0.99) to −112 ml · min^{-1} · °C^{-1} (r^2 = 0.96). From Kim *et al.*[164]; used with permission. Copyright © 1998, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

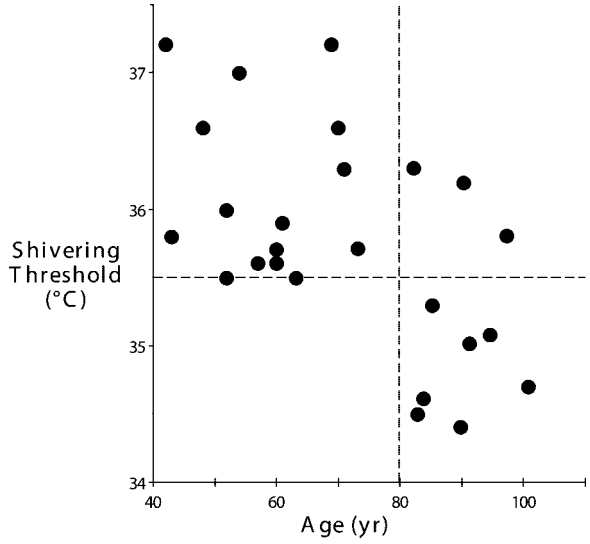

Fig. 18. Fifteen patients aged younger than 80 yr (58 ± 10 yr) shivered at 36.1° ± 0.6°C during spinal anesthesia; in contrast, eight patients aged 80 yr or older (89 ± 7 yr) shivered at a significantly lower mean temperature, 35.2° ± 0.8°C. The shivering thresholds in five of the eight patients aged older than 80 yr was less than 35.5°C, whereas the threshold equaled or exceeded this value in all the younger patients. Results are presented as mean ± SD. From Vassilieff *et al.*[85]; used with permission. Copyright © 1995, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

body paralysis (fig. 17).[125] Thermoregulatory defenses, once triggered, are thus less effective than usual during regional anesthesia.

Sedative and analgesic medications all impair thermoregulatory control to some extent.[109,127,137,161] Such inhibition may be severe when combined with the intrinsic impairment produced by regional anesthesia and other factors, including advanced age or preexisting illness (fig. 18).[85]

Interestingly, core hypothermia during regional anesthesia may not trigger a perception of cold.[43,162] The reason is that thermal perception (behavioral regulation) is largely determined by skin rather than core temperature.[78] During regional anesthesia, core hypothermia is accompanied by a real increase in skin temperature. The paradoxical result is often a perception of continued or increased warmth, accompanied by autonomic thermoregulatory responses, including shivering (fig. 19).[43,162]

Taken together, these data indicate that neuraxial anesthesia inhibits numerous aspects of thermoregulatory control. The vasoconstriction and shivering thresholds are reduced by regional anesthesia,[43,156–158,163] and further reduced by adjuvant drugs[109,137] and advanced age.[85] Even once triggered, the gain and maximum response intensity of shivering are approximately half normal.[164] Finally, behavioral thermoregulation is impaired.[162] The result is that cold defenses are triggered at a lower temperature than normal during regional anesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypo-

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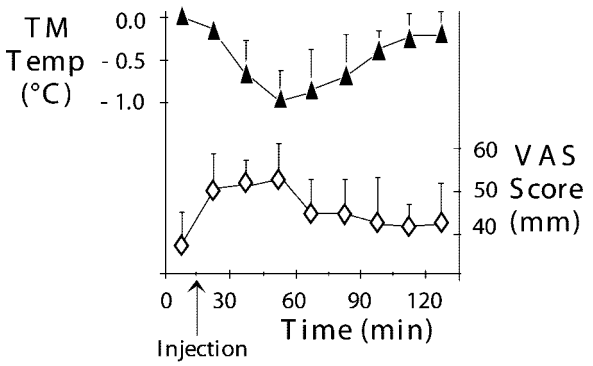

Fig. 19. Changes in tympanic membrane (TM) temperatures and thermal comfort (millimeters on a visual analog scale [VAS]) after epidural lidocaine injections in six volunteers in a cool operating room environment. Epidural injections were given after a 15-min control period. Shivering (not shown) started when tympanic temperature decreased approximately 0.5°C and continued until core temperature returned to within 0.5°C of control. Thermal comfort increased after epidural injections in each volunteer; maximal comfort occurred at the lowest core temperature. Results are presented as mean ± SD. From Sessler and Ponte[43]; used with permission. Copyright © 1990, the American Society of Anesthesiologists, Inc. and Lippincott Williams & Wilkins.

thermic. Because core temperature monitoring remains rare during regional anesthesia,[44] substantial hypothermia often goes undetected in these patients.[42]

Shivering during Neuraxial Anesthesia

Shivering-like tremor is common during neuraxial anesthesia and has at least four potential etiologies: (1) normal thermoregulatory shivering in response to core hypothermia, (2) normal shivering in normothermic or even hyperthermic patients who are developing a fever, (3) direct stimulation of cold receptors in the neuraxis by injected local anesthetic, and (4) nonthermoregulatory muscular activity that resembles thermoregulatory shivering. However, other etiologies remain possible. For example, a convincing cause has yet to be identified for the intense shivering that so often occurs immediately after induction of spinal or epidural anesthesia for cesarean delivery—well before core temperature has had time to decrease.

Most shivering associated with neuraxial anesthesia seems to be normal shivering, the expected response to hypothermia. And at least in volunteers given neuraxial anesthesia, shivering is always preceded by core hypothermia and vasoconstriction (above the level of the block).[43] Furthermore, electromyographic analysis indicates that the tremor has the 4- to 8-cycles/min waxing-and-waning pattern that characterizes normal shivering.[160] Fever is defined by a regulated increase in thermoregulatory response thresholds and can thus provoke shivering even in normothermic individuals. Nonetheless, perioperative fever is probably a relatively rare cause of shivering.

All mammals and birds have spinal thermoreceptors. There is thus the theoretical possibility that injection of relatively cool (*i.e.*, ambient temperature) local anesthetic into the epidural space might provoke shivering by stimulating local temperature sensors. Consistent with this possibility, the incidence of shivering in pregnant women was reported to be greater when they are given refrigerated epidural anesthetic than when the anesthetic is warmed before injection.[165] However, epidural administration of large amounts of ice-cold saline does not trigger shivering in nonpregnant volunteers.[166] Furthermore, the incidence of shivering is comparable in volunteers[43] and nonpregnant patients[167] given warm or cold epidural anesthetic injections. These data indicate that temperature of injected local anesthetic rarely provokes shivering during major conduction anesthesia.

Not all shivering-like tremor is thermoregulatory. It is possible to detect low-intensity shivering-like muscular activity both in surgical patients[168] and during labor.[169] The cause of this muscular activity remains unknown, but it is associated with pain and may thus result from sympathetic nervous system activation.[170]

Because skin temperature contributes to control of thermoregulatory responses, shivering of any type can be treated by warming the skin surface.[171] This is why shivering so often stops in a matter of seconds after a person enters a warm room even though core temperature has not had time to change at all. However, because the entire skin surface contributes 20% to thermoregulatory control[76,89] and the lower body contributes approximately 10%,[163] sentient skin warming is likely to only compensate for small reductions in core temperature. As might thus be expected, skin warming is only effective in a fraction of patients.

Most often, pharmacologic treatments will be required for moderate or severe shivering. The same drugs that are effective for shivering after general anesthesia can be used to treat shivering during neuraxial anesthesia. These include meperidine (25 mg, intravenously or epidurally),[172] clonidine (75 μg, intravenously),[173] ketanserin (10 mg, intravenously),[173] and magnesium sulfate (30 mg/kg, intravenously).[174]

Hyperthermia during Epidural Analgesia

Prolonged epidural analgesia for labor and delivery is occasionally associated with hyperthermia, typically to 38.5°–39.5°C. Hyperthermia develops only in a subset of women.[175] Hyperthermia typically develops after at least 5 h of labor and then increases over time.[176–179] The clinical consequence of this hyperthermia is that women given epidural analgesia for labor are more often given antibiotics than are those treated conventionally, and their offspring are more commonly treated for sepsis.[177,180,181]

Although best studied and most concerning in the context of labor, the association between epidural analgesia and hyperthermia is by no means restricted to labor; it also occurs in nonpregnant postoperative patients.[182] It is thus apparent that this hyperthermia is not

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restricted to pregnancy and must have a more general etiology.

There are several potential explanations for hyperthermia during labor analgesia. For example, it could simply be passive hyperthermia resulting from excessive heat production and inadequate heat dissipation to the environment. Labor certainly involves muscular effort that increases metabolic rate; furthermore, maternal metabolism is already increased by the fetus. Nonetheless, maternal metabolic rate remains small compared with even gentle exercise, which perhaps doubles metabolic rate, and does not provoke hyperthermia in any but the most extreme environments. There is not reason to believe that epidural analgesia *per se* alters whatever increase in metabolic rate that might normally accompany labor. And of course metabolic rate is near normal in postoperative patients who also develop hyperthermia with epidural analgesia.

A dense epidural block would inhibit sweating, which is sympathetically mediated, in the blocked region, but epidural analgesia for labor does not normally produce a sufficiently dense block. Furthermore, in a relatively dry and cool hospital environment, patients could easily dissipate many times their basal metabolic rates just from the upper body. It thus seems unlikely that an imbalance between heat production and loss is the explanation for hyperthermia during labor analgesia. A corollary is that hyperthermia during labor analgesia is a regulated fever rather than simple passive hyperthermia.

Hyperthermia during labor could just be the normal febrile response to infection. "Fever workups" and antibiotic treatments are common responses to maternal hyperthermia, and some hyperthermia surely is infectious fever.[183] Nonetheless, typical epidural-associated hyperthermia seems unlikely to result from infection, and the current consensus is that infection is rarely the cause.

Inflammation is a different matter, though. There are many potential sources of noninfectious inflammation in laboring patients, to say nothing of postoperative patients who obviously have injured tissues. For example, Dashe *et al.*[184] concluded, "Epidural analgesia is associated with intrapartum fever, but only in the presence of placental inflammation." It seems likely that inflammation provokes a regulated febrile response during labor and in postoperative patients. Consistent with this theory, high-dose steroids—powerful antiinflammatory drugs—nearly eliminate fever during labor.[185] In contrast, acetaminophen did not prevent hyperthermia, although the drug is usually an effective antipyretic.[186] That prolonged labor is associated with a greater risk of hyperthermia is consistent with a longer period in which to develop inflammation, especially placental inflammation, which is likely to release a variety of pyrogenic cytokines.[187]

The difficulty is that epidural analgesia surely does not augment the general inflammatory response to labor or surgery. Nor does it increase the risk of fetal malposition or need for cesarean delivery.[188] It thus remains unclear why epidural analgesia augments the risk of hyperthermia during labor and in postoperative patients. The conventional assumption is that hyperthermia is somehow caused by the technique; although no even slightly convincing mechanism has been proposed.

It is worth remembering, though, that when hyperthermia during labor is studied, pain in the "control" patients is usually treated with opioids—which themselves blunt thermoregulatory defenses[109,127] and specifically attenuate fever.[108] Fever associated with infection or tissue injury might then be suppressed by low doses of opioids that are usually given to the "control" patients while being expressed normally in patients given epidural analgesia.[189] The extent to which this mechanism contributes remains to be determined, and the theory is controversial.[190] However, no convincing alternative explanation has been advanced.

Summary

Core temperature, while by no means completely characterizing body heat content and distribution, is the best single indicator of thermal status in humans. Core temperature can be accurately monitored at the tympanic membrane, pulmonary artery, distal esophagus, and nasopharynx. Under appropriate circumstances, core temperature can also be reliably estimated from the mouth, axilla, and bladder. In contrast, infrared aural canal ("tympanic") and temporal artery systems are insufficiently accurate for clinical use.

Body temperature should be monitored in most patients undergoing general anesthesia exceeding 30 min in duration and in all patients whose surgery lasts longer than 1 h. Measuring body temperature (and maintaining normothermia) is now the standard of care during prolonged general anesthesia, especially for large operations where the risk of hypothermia is substantial. Core temperature should also be measured during regional anesthesia in patients likely to become hypothermic, including those undergoing body cavity surgery.

The processing of thermoregulatory information occurs in three phases: afferent thermal sensing, central regulation, and efferent responses. TRPV and TRPM receptors may be the fundamental temperature sensing elements. Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. The hypothalamus, other parts of the brain, the spinal cord, deep abdominal and thoracic tissues, and the skin surface each contribute roughly a fifth of the total thermal input to the central regulatory system.

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Temperature is regulated by central structures that compare integrated thermal inputs from the skin surface, neuraxis, and deep tissues with thresholds (triggering core temperatures) for each thermoregulatory response. The slope of response intensity *versus* core temperature defines the gain of a thermoregulatory response. Maximum intensity is defined by response intensity that no longer increases with further deviation in core temperature. The interthreshold range (core temperatures not triggering autonomic thermoregulatory responses) is bounded by the sweating threshold at its upper end and by the vasoconstriction threshold at the lower end. The interthreshold range is usually only 0.2°–0.4°C in humans, and that range defines normal body temperature.

Behavioral regulation is the most powerful thermoregulatory effector, and it is behavioral regulation that allows humans to tolerate extreme environments. However, surgical patients largely depend on autonomic responses, including sweating, vasoconstriction, and shivering. Among these defenses, vasoconstriction is the most important and accounts for most perioperative thermal perturbations.

Hyperthermia is any increase in core temperature; in contrast, fever is a regulated increase in the core temperature targeted by the thermoregulatory system. Fever is mediated by circulating endogenous pyrogens and is an active process. Hyperthermia can result from a variety of causes, many of which are serious, including infection, mismatched blood transfusion, allergic reactions, and malignant hyperthermia. Perioperative hyperthermia thus deserves a serious diagnostic effort, and often intervention.

General anesthetics and opioids have little influence on sweating but profoundly reduce the vasoconstriction and shivering thresholds. The result is a 10- to 20-fold increase in the interthreshold range. In contrast, general anesthetics have relatively little effect on the gain and maximum intensity of thermoregulatory responses. It is thermoregulatory impairment, not—as one might assume— exposure to a cool operating room environment, that causes most perioperative thermal perturbations. Thermoregulatory defenses are reasonably well maintained in infants and children but somewhat impaired in the elderly.

Central thermoregulatory control is slightly impaired by neuraxial anesthesia, but this is combined with reduced gain and maximum response intensity of shivering. Autonomic impairment is compounded by an impairment of behavioral regulation so that patients do not recognize that they are hypothermic. The result is that patients undergoing neuraxial anesthesia typically become hypothermic and do not sense the hypothermia. Temperature should thus be measured in patients undergoing major surgery during regional anesthesia, and they should be actively warmed as necessary to maintain normothermia.

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