Perioperative thermoregulation and heat balance

Daniel I Sessler

Core body temperature is normally tightly regulated to within a few tenths of a degree. The major thermoregulatory defences in humans are sweating, arteriovenous shunt vasoconstriction, and shivering. The core temperature triggering each response defines its activation threshold. General anaesthetics greatly impair thermoregulation, synchronously reducing the thresholds for vasoconstriction and shivering. Neuraxial anaesthesia also impairs central thermoregulatory control, and prevents vasoconstriction and shivering in blocked areas. Consequently, unwarmed anaesthetised patients become hypothermic, typically by 1–2°C. Hypothermia results initially from an internal redistribution of body heat from the core to the periphery, followed by heat loss exceeding metabolic heat production. Complications of perioperative hypothermia include coagulopathy and increased transfusion requirement, surgical site infection, delayed drug metabolism, prolonged recovery, shivering, and thermal discomfort. Body temperature can be reliably measured in the oesophagus, nasopharynx, mouth, and bladder. The standard-of-care is to monitor core temperature and to maintain normothermia during general and neuraxial anaesthesia.

Lancet 2016; 387: 2655–64

Published Online January 7, 2016 http://dx.doi.org/10.1016/S0140-6736(15)00981-2

Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA (Prof D I Sessler MD)

Correspondence to: Daniel I Sessler, Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave—P77, Cleveland, OH 44195, USA
ds@or.org

Normal thermoregulation

Normal core body temperature varies by at least 1°C based on circadian and menstrual cycles.[1] But at any given time, core temperature is tightly regulated, to within a few tenths of a degree during the day[2] with slightly more variability at night.[3] There are three major components to the control of body temperature: (1) afferent sensing, (2) central regulation, and (3) autonomic and behavioural defences (figure 1).

Temperatures are sensed peripherally and throughout the body by various receptors and nerves, with transient receptor potential proteins being the most important. Among them, TRPV receptors 1–4 are activated by heat whereas TRPM8 and TRPA1 are activated by cold.[4] Many transient receptor potential receptors are also activated by noxious stimuli.[5] Transient receptor potential receptors were identified only recently and the specific actions of various receptors remain under investigation. Thermoregulatory signals are primarily conveyed centrally via tracks in the anterior spinal cord, but there is considerable redundancy and multiple independent pathways apparently contribute to overall thermoregulatory control.[6]

Central thermoregulatory control is based on thermal input from structures throughout the body, which is integrated by the spinal cord, brain, and especially the hypothalamus. Roughly speaking, the skin surface, other peripheral tissues, core body temperature, the spinal cord, and the hypothalamus each contribute similarly to autonomic control. However, mean skin temperature contributes about 50% to thermal comfort,[7] with the upper chest and face contributing more than other regions.[8] Thermoregulatory control depends on instantaneous core temperature, rather than the rate of change of core temperature;[2] by contrast, rapid changes in skin temperature provoke disproportionately large responses,[9] but only at rates exceeding 6°C/h.[10]

Efferent–effector thermoregulatory functions can broadly be divided into behavioural and autonomic responses. Behaviour, which includes all volitional responses to thermal discomfort, is by far the most powerful.[11] Behavioural responses range from protective positioning and clothing, to building shelters and air conditioning. Behavioural thermoregulation enables human beings to tolerate the wide variety of environments we inhabit.

The primary autonomic thermoregulatory defences in human beings are active precapillary vasodilation and sweating,[12] arteriovenous shunt vasoconstriction,[13] and shivering.[14] Non-shivering thermogenesis (activation of brown fat by an uncoupling protein, thermogenin[15]) is used in preference to shivering in infants.[16] In adults, non-shivering thermogenesis might contribute to long-term energy homoeostasis,[17,18] but is not an important thermoregulatory defence.[19]

Even non-athletic adults can produce a litre of sweat per hour and dissipate more than ten times their basal metabolic rate in a dry convective environment.[20] Thermoregulatory vasoconstriction is largely restricted to arteriovenous shunts in the limbs (mostly fingers and toes). These 100-µm vessels convey 10 000 times as much blood as 10-µm capillaries when dilated, and essentially none when constricted. Although anatomically restricted to fingers and toes, they affect blood flow to entire extremities and are effective at dissipating heat when open and constraining metabolic heat to the core when closed.[21]

Shivering can rapidly augment metabolic rate by a factor of about five,[22] and sustain a three-times increase for 3–4 h before muscles tire.[23] However, shivering can be

Search strategy and selection criteria

I supplemented my collection of published articles by searching MEDLINE with ("temperature" or "thermoregulation") and ("anaesthesia" or "surgery") for articles published between 2000 and 2014, with no language restrictions. I also considered relevant references from within citation lists. All articles were considered; those with the most robust methodology and largest sample size were given most weight. In general, the most recent reliable evidence is cited. Major reviews are cited to provide additional details and references. I selected articles for inclusion on the basis of my impression of their importance.

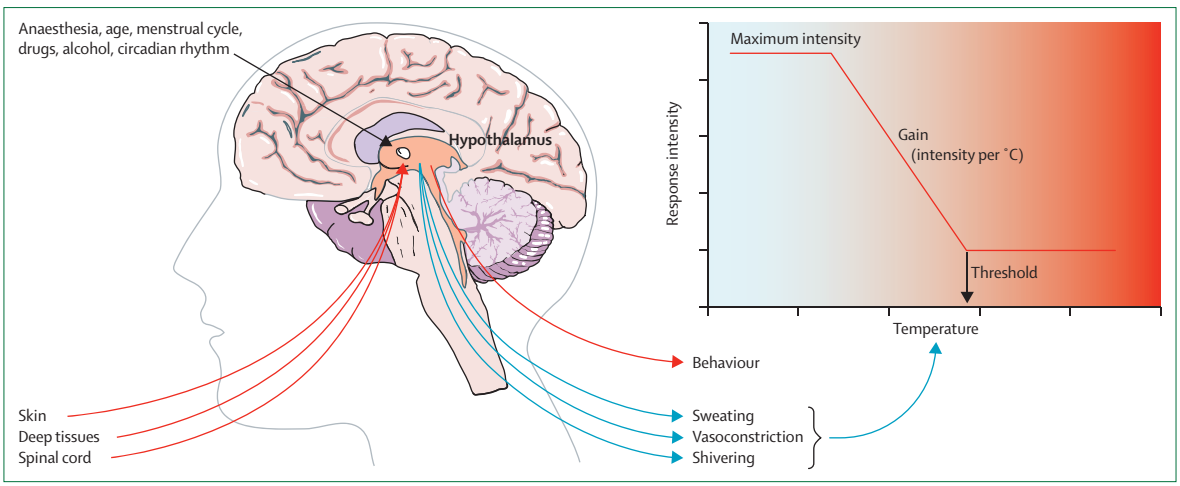

Figure 1: **Regulation of temperature in human beings**
Temperature is sensed at the skin surface, in deep tissues, the spinal cord, the brain, and the hypothalamus. Integration of thermal input occurs at various levels, but the hypothalamus is the most important controller in mammals. The most important efferent autonomic responses are sweating, arteriovenous shunt vasoconstriction, and shivering. Behavioural responses (any volitional responses) are by far the strongest defences, but not usually available to surgical patients. Each response is characterised by its threshold (triggering core temperature), gain (increase in response intensity with further deviation in core temperature), and maximum response intensity.

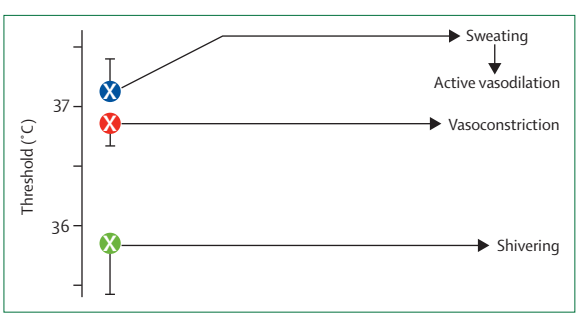

Figure 2: **The major thermoregulatory defence thresholds in human beings**[2]
Temperatures between the sweating and vasoconstriction thresholds define the inter-threshold range, usually a few tenths of a degree, which do not activate thermoregulatory defences and thus define normal core temperature (between the red and blue circles). Sweating activates active precapillary vasodilation, which moves heat towards the skin surface for dissipation to the environment. The shivering threshold is 1°C below the vasoconstriction threshold; thus, by the time human beings begin to shiver, they are already fairly hypothermic.

less effective than might be expected because much of the muscular activity is in the extremities. Thus, the vasodilation necessary to oxygenate peripheral muscles counteracts thermoregulatory vasoconstriction and so, at least to some extent, permits metabolic heat to move from the core to peripheral tissues, and from there to the environment.

Each thermoregulatory response has a threshold (a triggering core temperature), gain (increase in response intensity with core temperature deviation beyond the triggering threshold), and a maximum response intensity. Precapillary vasodilation and sweating responses are generally synchronous—ie, they have the same triggering core temperature. The threshold for the initial cold defence, vasoconstriction, is normally just a few tenths of a degree below the sweating threshold. By contrast, the shivering threshold is typically about 1°C below the vasoconstriction threshold. Temperatures between the sweating and vasoconstriction thresholds, the inter-threshold range, define normal temperatures—usually about 37°C (figure 2). Core temperatures are usually slightly greater in women than in men, and vary by about 1°C on a circadian basis.

Because the sweating and vasoconstriction thresholds differ only slightly, the thermoregulatory system has sometimes been modelled as a setpoint, much like a thermostat that is either off or on. However, this approach does not account for sequential activation of defences or for the effects of drugs on thermoregulatory control. In addition to anaesthetics and anaesthetic adjuvants, various drugs including ethanol (mostly behavioural),[24] amphetamines,[25] and buspirone,[26] impair thermoregulatory control.

Thermoregulation is well developed at birth, and even premature infants regulate temperature better than might be expected. However, small thermal mass and high surface-area-to-weight ratio make infants more susceptible to environmental perturbations than adults. Regulation is also relatively well maintained in elderly people, which might be because behavioural regulation compensates for reduced efficacy of autonomic responses.

General anaesthesia and thermoregulation

Volatile anaesthetics such as isoflurane and sevoflurane,[27] the inhaled anaesthetic nitrous oxide,[28] intravenous anaesthetics such as propofol,[29] and opioids[30] all substantially impair thermoregulatory control. None of these drugs has much effect on sweating thresholds, but each greatly and synchronously reduces the vasoconstriction and shivering thresholds. Threshold reductions are concentration dependent over the entire clinical range, and the slopes vary between

drugs. Concentration-dependent reductions are linear for intravenous drugs, whereas impairment is disproportionate at higher concentrations of volatile anaesthetics. Thermoregulatory response thresholds are well preserved in infants and children,[31] but cold-defence thresholds are reduced by about 1°C in elderly people.[32] Even infants do not activate non-shivering thermogenesis during anaesthesia.[33]

With typical combinations and doses of drugs used for general anaesthesia, the vasoconstriction threshold decreases to around 34·5°C. The consequence is that the inter-threshold range, which normally spans only a few tenths of a degree, increases by a factor of 10–20 during general anaesthesia. Anaesthetised patients are thus poikilothermic over a broad range of core temperatures. But when core temperature exceeds the sweating threshold or decreases to below the vasoconstriction threshold, anaesthetised patients will activate thermoregulatory defences. Figure 3 shows how the inter-threshold range increases greatly as a function of anaesthetic drug concentration.

Volatile anaesthetics reduce the gain of vasoconstriction, but shunt flow nonetheless decreases to nearly zero (appendix).[36] Thus, even during anaesthesia, thermoregulatory vasoconstriction effectively constrains metabolic heat to the core thermal compartment. General anaesthesia obscures the normal pattern of shivering and somewhat reduces maximum shivering intensity.[37] By contrast, the gain and maximum intensity of shivering are maintained during opioid use.[38] Sedatives such as midazolam,[39] even combined with typical opioid doses, do not appreciably impair thermoregulatory control. Sweating remains largely intact during general anaesthesia.[40] Overall, most anaesthetic-induced impairment of thermoregulatory control results from reduced cold-response thresholds rather than from substantial effects on vasoconstriction or shivering, once triggered.

How anaesthetics impair thermoregulatory control is unknown. (For that matter, how anaesthetics produce unconsciousness remains speculative.) However, volatile anaesthetics directly inhibit TRPV1 receptors,[41] perhaps contributing both analgesia and reduced thermal input to central thermoregulatory systems.[42] The thermoregulatory effects of anaesthetic drugs seem to be state dependent, rather than affected by thermal history.[40]

Neuraxial anaesthesia and thermoregulation

Epidural anaesthesia results from injection of moderate amounts of local anaesthesia into the epidural space; spinal anaesthesia similarly results from injection of small amounts of local anaesthetic into the spinal canal. Both types of anaesthesia, termed neuraxial, prevent most efferent and afferent neural activity to the lower body. Although local anaesthetics used in neuraxial anaesthesia do not normally reach the brain, each type of block nonetheless impairs thermoregulatory control via three mechanisms.

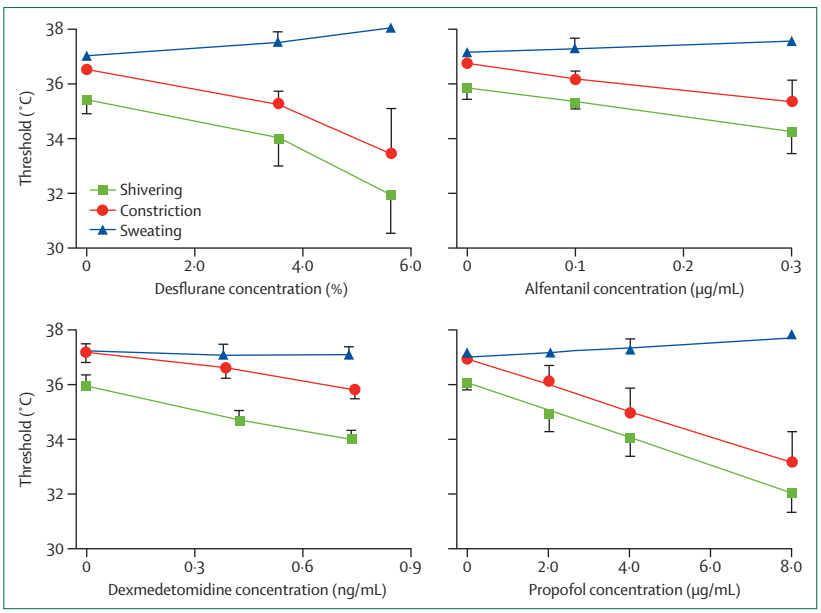

Figure 3: **The major autonomic thermoregulatory response thresholds in volunteers given desflurane,[34] alfentanil,[30] dexmedetomidine,[35] or propofol[29]**
Each drug slightly increases the sweating threshold (triggering core temperature) while greatly and synchronously decreasing the vasoconstriction and shivering thresholds. SD bars smaller than the data markers have been deleted. Reproduced with permission from Wolters Kluwer.

First, hypothermia does not provoke as much thermal discomfort as would be expected in the presence of neuraxial blocks.[43] Consequently, patients having epidural or spinal anaesthesia do not complain of feeling cold, even when they are hypothermic. The reasons are unclear, but possibly the central controller interprets lack of tonic cold signals from the legs as relative warmth.

Second, neuraxial anaesthesia impairs thermoregulatory control centrally, reducing the vasoconstriction and shivering thresholds, thus augmenting the inter-threshold range.[44] Neuraxial anaesthesia impairs central thermoregulatory control less than does general anaesthesia, and impairment is a linear function of block height—ie, higher blocks produce more thermoregulatory impairment (figure 4).[45] Central impairment is even apparent when epidural anaesthesia is induced with 2-chloroprocaine, a local anaesthetic that has a plasma half-life of only seconds, thus showing that the effect is peripherally mediated.[44] Why administration of local anaesthesia far from the brain impairs central thermoregulatory control is unknown, but again possibly results from the anaesthetic blocking tonic cold signals from the lower body.[46]

Third, all autonomic thermoregulatory defences are primarily neurally mediated. Thus, active vasodilation, sweating, vasoconstriction, and shivering all require intact nerves. Neuraxial anaesthesia not only blocks afferent pain signals, but also efferent nerves that control vasoconstriction and shivering. Thus, if they occur at all, gain and maximum intensity are substantially reduced.[47] The consequence is that patients given neuraxial

See Online for appendix

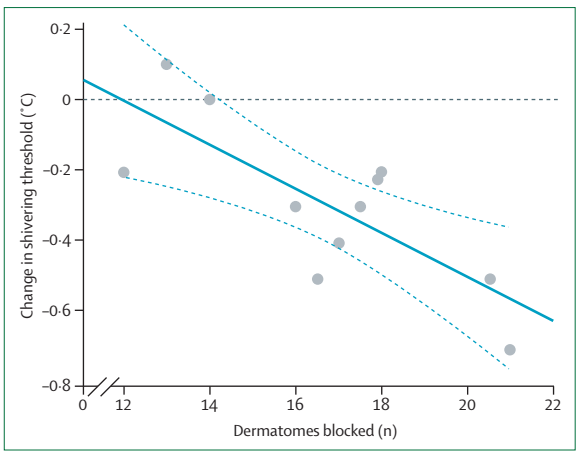

Figure 4: **Relation between the number of dermatomes blocked and the reduction in the shivering threshold**
There are 22 dermatomes: five sacral segments, five lumbar segments, and 12 thoracic segments. The shivering threshold is the difference between the control shivering threshold and spinal shivering 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 are 95% CIs. Adapted with permission from Leslie and Sessler.[45]

anaesthesia become as hypothermic as those given general anaesthesia for a similar operation. The thermoregulatory effects of general and neuraxial anaesthesia are roughly additive.[44]

By contrast with neuraxial anaesthesia, peripheral nerve blocks[48] do not have substantive thermoregulatory effects beyond preventing local thermoregulatory responses, all of which are neurally mediated.

Hyperthermia and fever

Hyperthermia is any elevation in core temperature. It can result from excessive heating, excessive heat production, inadequate heat loss, or setpoint elevation. Routine intraoperative warming systems can produce hyperthermia, especially during long operations. Hyperthermia is rare in adults using modern warming systems, but occasionally occurs in infants and children. Intraoperative hyperthermia can also result, either intentionally or not, from peritoneal lavage with heated chemotherapy solutions.

Examples of excessive heat production include vigorous exercise and malignant hyperthermia. Inadequate heat loss can result from high ambient temperature, especially when combined with high humidity, but can also occur when sweating is prevented by moisture-impervious clothing such as hazardous material suits. Hyperthermia from most of these causes is usually easy to treat: eliminate excessive heating and promote heat loss.

Fever is a type of hyperthermia, but differs from other core temperature elevations in being a regulated increase. It is mediated by circulating pyrogenic cytokines including interleukins[49] and interferon,[50] which are largely released from mononuclear inflammatory cells. Endogenous pyrogens activate the vagus nerve, triggering release of prostaglandin E2 in the preoptic-anterior hypothalamus, which in turn increases the setpoint.[51] Many drugs also provoke fever and hyperthermic syndromes.[52]

Fever is rare during anaesthesia because both volatile anaesthetics[53] and opioids[54] blunt the febrile response, but can occur in response to infection, allergy, and mismatched blood transfusions. After surgery, when the thermoregulatory effects of anaesthesia dissipate, fever is more likely. Fever is also common in critical care patients.

By contrast with passive hyperthermia, fever can be challenging to manage. Because core temperature is highly regulated, simply promoting heat loss—and even vigorous cooling—often fails. Active cooling in patients with fever provokes thermal discomfort, autonomic nervous system activation, and shivering.[55] Furthermore, it does not necessarily reduce core temperature, which remains regulated to a high temperature.[56] Aggressive treatment of fever might worsen outcomes.[57]

A better strategy is to treat the underlying cause (ie, infection) or use drugs such as paracetamol to block fever centrally,[58] thus converting fever to passive hyperthermia, which is easier to treat. However, in practice underlying causes are often unknown or untreatable—and even theoretically effective drugs do not blunt fever as well as might be hoped,[59] possibly because not all fever is mediated by prostaglandins.[60] Depending on the clinical situation, actively cooling febrile patients might be necessary, but cooling should be a last resort.

Heat balance

Human tissues can be divided into core and peripheral thermal compartments. The core compartment is generally defined as the tissues that have a high and nearly constant temperature over a wide range of environments and thermoregulatory responses. The core, mostly the trunk and head, constitutes about half the body mass. The remaining mass, mostly in the arms and legs, represents the peripheral thermal compartment. Although both core and peripheral temperatures influence central thermoregulatory responses, the core dominates. Consequently, core temperature is tightly regulated whereas peripheral tissue temperature is allowed to vary over a fairly wide range.[61] Peripheral tissues thus act as a thermal buffer, absorbing or dissipating heat as necessary to protect the core and prevent activation of thermoregulatory defences in response to small deviations in ambient temperature.

Over the long term, peripheral tissues must be cooler than the core because the second law of thermodynamics specifies that heat can only flow down a temperature gradient. Without a gradient, metabolic heat would be unable to flow peripherally and from there to the environment. At hospital ambient temperatures, peripheral tissues are normally 2–4°C cooler than the core, depending on vasomotor status, with arteriovenous shunt constriction promoting higher gradients.

The combination of anaesthesia-induced thermoregulatory impairment, cool operating rooms, and operative exposure makes most unwarmed surgical patients hypothermic. Among these factors, by far the most important is thermoregulatory impairment since non-anaesthetised adults would otherwise easily resist surgical heat loss. Hypothermia in unwarmed surgical patients develops with a characteristic three-phase pattern (appendix).

In the first hour after induction of general anaesthesia, core temperature decreases rapidly—far too fast to be explained by heat loss to the environment alone. This rapid reduction in core temperature results from anaesthetic-induced vasodilation, which allows heat to redistribute from core to peripheral tissues (vasodilation results largely from impairment of central thermoregulatory control rather than from direct peripheral effects of anaesthetics). Redistribution hypothermia does not alter body heat content or mean body temperature, but does substantially reduce core temperature because peripheral tissues are warmed at the expense of the core. The flow of heat is substantial and is the major initial cause of core hypothermia during both general[62] and neuraxial[63] anaesthesia (appendix).

Redistribution hypothermia is typically followed by a slower linear reduction in core temperature that results from heat loss to the environment exceeding metabolic heat production. The primary mechanisms of intraoperative heat loss are radiation and convection; conduction and evaporation usually contribute little. Heat loss from within surgical incisions probably also contributes, but its magnitude has yet to be quantified in human beings. The rate at which temperature decreases is a function of the difference between heat loss and production. It thus depends on ambient temperature, size of the operation, and the extent to which patients are insulated or actively warmed.

In patients who become sufficiently hypothermic, core temperature plateaus; no matter how large the operation or how much longer it lasts (appendix), temperature no longer decreases. The core temperature plateaus either passively, when heat loss and production are balanced, or when patients become sufficiently hypothermic to activate thermoregulatory vasoconstriction, usually at about 34·5°C during general anaesthesia. Once activated, arteriovenous shunt constriction is effective, constraining metabolic heat to the core, thus preventing further core hypothermia. However, heat loss from peripheral tissues continues, and body heat content therefore continues to decrease.[64]

Patients are most at risk of intraoperative hypothermia when general and neuraxial anaesthesia are combined because the thermoregulatory impairment induced by each is additive. During combined anaesthesia, the vasoconstriction threshold is reduced by the sum of the independent effects of each anaesthetic approach; furthermore, each type of anaesthesia reduces the gain and maximum intensity of vasoconstriction. The result is that patients having combined anaesthesia become colder before they activate thermoregulatory defences than do patients having general anaesthesia alone. And, once activated, defences in patients undergoing combined anaesthesia are less effective than usual in preventing further core hypothermia.[44] Perioperative heat balance has been reviewed in detail previously.[65]

Consequences of mild perioperative hypothermia

Most cellular functions are temperature dependent. Furthermore, hypothermia provokes systemic responses, some of which are potentially harmful. Thus, even mild hypothermia causes various complications. Although few patients are susceptible to all potential complications, most are susceptible to at least some. Throughout this section, hypothermia will refer to a 1–2°C reduction in core temperature unless otherwise specified. Most trials were done in the 1990s, when patient warming was rare; thus, the comparisons were routine management versus extra warming.

The best-documented complication of hypothermia is coagulopathy. It results mostly from a reversible impairment of platelet aggregation via reduced release of thromboxane A3,[66] which reduces formation of an initial platelet plug. However, hypothermia also impairs the function of enzymes in the coagulation cascade, which reduces clot formation (hypothermia-induced coagulopathy is not apparent from routine testing because laboratories perform tests at 37°C rather than at the patient's actual temperature).[67] The combination of platelet and enzyme impairment substantially increases perioperative blood loss.

Numerous trials, summarised in a meta-analysis,[68] have consistently shown that even 1°C hypothermia significantly increases blood loss by about 20%. Hypothermia-related coagulopathy also increases the need for transfusion, with the odds of requiring red blood cells increasing similarly.[68]

All surgical wounds become contaminated. Whether contamination progresses to infection is mostly determined by host defence. There are at least three mechanisms by which perioperative hypothermia impairs host defence. First, even mild hypothermia triggers postoperative vasoconstriction. Vasoconstriction constrains metabolic heat to the core and speeds rewarming, but it can simultaneously reduce perfusion to wounded tissue which, in turn, reduces tissue oxygen partial pressure (even when blood is fully saturated). Tissue oxygenation is important because molecular oxygen is required for oxidative killing by neutrophils, the primary defence against bacterial contamination. Second, hypothermia reduces systemic immune activation and decreases motility of key cells including macrophages. Third, hypothermia reduces tissue healing, which is necessary to prevent wound dehiscence and recontamination.

Consistent with these mechanisms, in a study of wound infections and temperature, 200 patients having colorectal surgery randomly assigned to normothermia were far less likely to develop incisional infections (6%) than those allowed to become 2°C hypothermic (19%).[69] Only one subsequent major trial has reported that either local wound or systemic warming comparably reduced infection risk.[70] However, this study is difficult to interpret because core temperature was unreported.

Given the thermal sensitivity of enzymes, it is unsurprising that even mild hypothermia prolongs the action of various drugs. The duration of action of vecuronium (a non-depolarising muscle relaxant) is doubled by 2°C hypothermia.[71,72] The effect on other drugs is less, but still substantial. For example, 3°C hypothermia prolongs the duration of atracurium, another muscle relaxant, by 60%,[73] and increases plasma propofol concentrations by 28%, largely as a result of reduced hepatic blood flow.[73] A predictable consequence of delayed drug disposition is that postanaesthetic recovery is prolonged in hypothermic patients.[74]

Vasoconstriction is effective even during anaesthesia. Consequently, core temperature rarely decreases the additional 1°C necessary to reach the shivering threshold. Furthermore, many anaesthetised patients are given muscle relaxants so shivering is rare during surgery.[14] By contrast, postoperative shivering is common in hypothermic patients. Rhythmic involuntary muscular activity after surgery is largely thermoregulatory, but is aggravated by volatile anaesthetics. Some patient also show low-intensity shivering-like muscular activity that is not thermoregulatory[75] and seems to be aggravated by pain.[76]

Trials suggest that at least a dozen drugs are effective for treatment of postoperative shivering.[77] The presumed mechanism is reduction of the shivering threshold, and the most commonly used treatments, such as pethidine,[78] clonidine, dexmedetomidine,[79] and ketamine, lower the core temperature that triggers shivering. However, formal assessments of thermoregulation suggest that some reportedly effective drugs, including magnesium,[80] doxapram,[81] and ondansetron,[82] cause little if any reduction in the shivering threshold. How these drugs treat shivering thus remains unclear, but it is possible that tiny reductions in the shivering threshold are sufficient when patients are only slightly hypothermic.

A predictable consequence of intraoperative hypothermia is postoperative thermal discomfort. Feeling cold after surgery is not life-threatening, but nor are pain or nausea and vomiting, yet considerable effort is invested in preventing and treating both. Thermal discomfort is typically intense, and untreated patients who are 2°C hypothermic at the end of surgery take 2 h to return to normothermia and thermal comfort. Anecdotal experience suggests that, unlike pain and nausea, memories of postoperative thermal discomfort remain intense for years after surgery. Active cutaneous warming greatly improves thermal comfort in hypothermic patients and simultaneously speeds rewarming, but prevention of hypothermia is an obviously preferable management strategy.

Among inpatients older than 45 years of age having routine non-cardiac surgery the incidence of myocardial injury (mostly infarctions) is about 9%; mortality is 10%, making myocardial injury the leading cause of death in these patients.[83] There are several putative mechanisms by which mild perioperative hypothermia might contribute to myocardial injury. For example, hypothermia augments plasma norepinephrine concentration 700% with 1·3°C of hypothermia[84] and promotes vasoconstriction with consequent hypertension and tachycardia.[85]

The effects of hypothermia on morbid perioperative outcomes were reported in a study of 300 vascular surgery patients. This study, reported in 1996, was based on 48-h electrocardiogram monitoring, which was the best technology available at the time. However, it is now known—based on troponin monitoring—that the method is insensitive. And consistent with this understanding, the reported incidence of myocardial infarction was 1%, which is more than ten-times too low. The extent to which mild hypothermia contributes to perioperative myocardial injury thus remains unclear, although the risk is probably substantial. The table shows major randomised trials that assessed complications of mild perioperative hypothermia.

Maintaining normothermia

Mean body temperature remains unchanged as long as metabolic heat production equals heat loss to the environment. Human beings normally have no difficulty balancing heat loss and production in hospital environments, but environmental heat loss can be substantial during surgery, and general anaesthesia reduces metabolic heat production by about 30%. Furthermore, core-to-peripheral redistribution of heat during the first hour of anaesthesia reduces core temperature even though body heat content remains unchanged. Perioperative thermal management is thus challenging, and nearly all unwarmed surgical patients become hypothermic.

Even patients who are actively warmed initially develop core hypothermia from redistribution hypothermia.[91] Typically, core temperature decreases during the first hour of anaesthesia; thereafter, core temperature gradually increases (or continues to decrease) with a slope that depends on ambient temperature, size of the operation, patient morphometric characteristics, and efficacy of insulation or active warming. Various perioperative warming devices are available, which can broadly be divided into passive insulation and active warming through systems that warm the skin surface, heated fluids, warm inspired or peritoneal gases, and endovascular heat exchangers.

	N	ΔT_{core} (°C)	Normothermic	Hypothermic	p value	Reference
Surgical wound infection	200	1·9	6%	19%	<0·01	Kurz et al[69]
Duration of stay in hospital	200	1·9	12·1 days (SD 4·4)	14·7 days (SD 6·5)	<0·01	Kurz et al[69]
Ventricular ectopy	300	1·3	2%	8%	<0·05	Frank et al[86]
Urinary excretion of nitrogen	12	1·5	728 mmol per day (SD 254)	1240 mmol per day (SD 558)	<0·05	Carli et al[87]
Duration of vecuronium	20	2·0	28 min (SD 4)	62 min (SD 8)	<0·001	Heier et al[88]
Duration of atracurium	6	3·0	44 min (SD 4)	68 min (SD 7)	<0·05	Leslie et al[73]
Plasma propofol concentration	6	3·0	100%	128%	<0·05	Leslie et al[73]
Duration of postanaesthetic recovery	150	1·9	53 min (SD 36)	94 min (SD 65)	<0·001	Lenhardt et al[74]
Change in plasma norepinephrine	9	1·3	–0·6 µg/mL (SD 1·0)	46 µg/mL (SD 5)	<0·05	Frank et al[89]
Thermal discomfort	74	2·6	50 mm VAS (SD 10)	18 mm VAS (SD 9)	<0·001	Kurz et al[90]

Only randomised trials of people are included. Subjective responses were evaluated by observers masked to treatment group and core temperature. N=total number of participants. ΔT_{core}=difference in core temperature between the treatment groups. VAS is a 100 mm long visual analogue scale (0 mm=intense cold, 100 mm=intense heat). Studies of blood loss and transfusion requirement are excluded because they are summarised in a meta-analysis.[68] Dozens of studies, not shown, demonstrate that hypothermia provokes postoperative shivering.

Table: **Major in-vivo consequences of mild perioperative hypothermia in human beings**

A single layer of passive insulation reduces cutaneous heat loss by 30% at typical operating room temperatures. The type of insulation matters little, since the major heat loss barrier is actually the layer of still air trapped below the insulator. A 30% reduction in heat loss is clinically important and roughly compensates for the anaesthesia-induced reduction in metabolic heat production. Of course, the effect of insulation is restricted to covered surfaces. Unfortunately, adding additional layers of insulation provides little additional benefit. For example, three layers of passive insulation only halves heat loss.[92] Most surgical patients will become hypothermic with insulation alone, and require active intraoperative heating to maintain normothermia.

Most patients having surgery are actively warmed from the skin surface. This approach is attractive because skin is readily available, can be warmed safely, and because most heat is lost from the skin. Forced air,[93] resistive heating,[94] and circulating water[94] are the typical approaches, with forced air being by far the most commonly used, presumably because the approach is effective, inexpensive, and easy to use. Forced air is also safe because modest heat intensity is distributed over a large surface area and air never warms dependent regions, thus avoiding the dangerous combination of heat and pressure.

Redistribution hypothermia can partly be ameliorated by pre-warming patients. Warming patients before induction of anaesthesia does not much increase core temperature, which remains tightly regulated, but absorbed heat does increase the temperature of peripheral tissues, thus reducing the normal core-to-peripheral tissue temperature gradient.[61] To the extent that temperature of the peripheral thermal compartment approaches core temperature, there will be little core-to-peripheral flow of heat and consequent redistribution hypothermia.[95] Typically, core temperature in pre-warmed patients stays about 0·4°C warmer than it does in those who are not pre-warmed.

Fluid warming cannot meaningfully warm patients because intravenous or irrigation fluids can only slightly exceed core temperature. Fluid warming therefore cannot compensate for redistribution hypothermia, much less for ongoing loss from the skin surface and from within surgical incisions. However, patients can be cooled considerably by infusion of unwarmed fluids. Each litre of fluid infused at ambient temperature reduces mean body temperature by 0·25°C in a 70 kg patient. A unit of refrigerated blood also reduces mean body temperature by 0·25°C (blood is half the volume, but twice as cold). Fluids should therefore be warmed before being given to patients in large volumes (ie, more than 1 L/h).

The heat capacity of air is low. The heat of vaporisation (required to humidify dry gases) is higher, but still low compared with the metabolic rate of patients. Consequently, little metabolic heat is lost through the airway. A corollary is that airway or peritoneal heating and humidification is unable to transfer meaningful amounts of heat into patients. Vascular heat-exchange catheters are expensive and invasive, but they also transfer far more heat than surface systems. Their use is largely restricted to therapeutic hypothermia in which rapid onset of controlled hypothermia is crucial.

Because numerous randomised trials have shown that hypothermia causes serious complications, maintaining intraoperative normothermia[96] has become a de-facto standard-of-care. For example, guidelines[97] of the British National Institute for Health and Care Excellence indicate that patient temperature should be measured at 30-min intervals during anaesthesia and that patients should be actively warmed to a target of 36·5°C. But how normothermia is maintained is strictly discretionary. Clinicians can select various approaches, or combinations of approaches, and any that safely keep patients normothermic are perfectly acceptable.

Temperature monitoring

Precision and accuracy of temperature monitoring depends on both the measurement system and the measurement site. There is no single body temperature; tissue temperatures vary greatly from site to site. The core thermal compartment (ie, the trunk and head) is highly perfused and relatively homogeneous. By contrast, peripheral (ie, arm and leg) tissue temperatures are typically well below core temperature, and skin temperatures are usually still lower. Skin temperatures also vary considerably from region to region, depending on the environment and thermoregulatory vasomotion.

Temperatures at various core, peripheral, and cutaneous sites are potentially important indicators of body heat content and most tissues provide afferent input to the central thermoregulatory system. Thus, mean body temperature well characterises overall thermal state,[98] but because it is estimated from the weighted average of measurements at many locations, its use is impractical for routine clinical care. Furthermore, core temperature contributes disproportionately to thermoregulatory control. The single temperature that best characterises a patient's thermal status is thus core temperature.

Four monitoring sites are considered to be core: the pulmonary artery, distal oesophagus, nasopharynx with the probe inserted 10–20 cm, and tympanic membrane as measured with a contact thermistor or thermocouple. These sites are largely interchangeable, rarely varying by more than a few tenths of a degree centigrade. In intubated patients, distal oesophageal temperatures are easy to obtain and highly resistant to artifact. In many patients, however, none of these temperatures is readily available.

Fortunately, other temperature monitoring sites are suitable for clinical use in selected patients. Among the best is the classical sublingual temperature, which remains a good estimate of core temperature.[99] Other sites that might be suitable include the axilla and bladder (especially when urine flow is adequate). The key is selecting an appropriate monitoring site (and method) in different circumstances. For example, oral temperatures will underestimate core temperature in someone who has just had a cold drink; similarly, axillary temperatures will underestimate the core if the probe is not positioned above the axillary artery and the arm adducted.

Skin temperature is generally well below core temperature. Forehead temperature is less variable than other cutaneous sites, but varies sufficiently with ambient temperature that simply adding a constant, such as 2°C, to skin temperature only poorly approximates core temperature.[100] Temperature of the external aural canal is essentially a skin temperature rather than an approximation of tympanic membrane temperature. Rectal temperature is in surprisingly poor equilibrium with the core, and can lag substantially, so it detects fever and other rapid thermal perturbations poorly.[101] Rectal temperatures are also artifactually elevated during exercise.

Accurate thermometers are readily available. For example, thermistors and thermocouples are inexpensive and accurate, and infrared systems accurately measure surface temperatures. The difficulty in most cases is getting monitors to body sites that represent or reasonably estimate core temperature. Almost always, the measurement site rather than the device determines precision and accuracy.

Cardiopulmonary bypass often causes rapid temperature perturbations. During bypass, especially the rapid cooling and rewarming phases, there can be substantial temperature differences even within the core thermal compartment, along with very large core-to-peripheral tissue temperature gradients. Therefore, temperatures taken at various sites might be needed to characterise a patient's thermal state.

The standard-of-care is to monitor body temperature in patients having general anaesthesia lasting more than 30 min, and in patients having large operations with neuraxial anaesthesia. Only temperature monitoring will identify patients with thermal disturbances. Although hypothermia is by far the most common intraoperative disturbance, hyperthermia and fever also occur. Failure to monitor temperature, for example, is strongly associated with mortality among patients having malignant hyperthermia crises.[102] Temperature monitoring is not normally needed for sedation alone or for peripheral nerve blocks because thermoregulatory control is well maintained during these procedures.

Recommendations

Both general and neuraxial anaesthesia greatly impair thermoregulatory control, with the consequence that unwarmed surgical patients become hypothermic. Randomised trials show that even mild hypothermia causes numerous severe complications. Core temperature should be monitored during general anaesthetics lasting more than 30 min and during neuraxial anaesthesia for substantial procedures. Surgical patients should be kept normothermic.

Declaration of interests

I serve on advisory boards for several companies that make patient warming systems, and consult for several others. These companies pay travel expenses for their out-of-town meetings, but I donate all fees to charity and thus have no personal financial interests related to this Review.

References

1 Sessler DI, Lee KA, McGuire J. Isoflurane anesthesia and circadian temperature cycles. *Anesthesiology* 1991; **75:** 985–89.

2 Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M. Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. *Anesthesiology* 1994; **80:** 780–88.

3 Tayefeh F, Plattner O, Sessler DI, Ikeda T, Marder D. Circadian changes in the sweating-to-vasoconstriction interthreshold range. *Pflügers Arch* 1998; **435:** 402–06.

4 Feketa VV, Zhang Y, Cao Z, et al. Transient receptor potential melastatin 8 channel inhibition potentiates the hypothermic response to transient receptor potential vanilloid 1 activation in the conscious mouse. *Crit Care Med* 2014; **42:** e355–63.

5 Premkumar LS, Abooj M. TRP channels and analgesia. *Life Sci* 2013; **92:** 415–24.

6 Fealey RD. Interoception and autonomic nervous system reflexes thermoregulation. *Handb Clin Neurol* 2013; **117:** 79–88.

7 Frank S, Raja SN, Bulcao C, Goldstein D. Relative contribution of core and cutaneous temperatures to thermal comfort, autonomic, and metabolic responses in humans. *J Appl Physiol* 1999; **86:** 1588–93.

8 Burke WEA, Mekjavic IB. Estimation of regional cutaneous cold sensitivity by analysis of the gasping response. *J Appl Physiol* 1991; **71:** 1933–40.

9 McCaffrey TV, Wurster RD, Jacobs HK, Euler DE, Geis GS. Role of skin temperature in the control of sweating. *J Appl Physiol* 1979; **47:** 591–97.

10 Taniguchi Y, Lenhardt R, Sessler DI, Kurz A. The effect of altering skin-surface cooling speeds on vasoconstriction and shivering thresholds. *Anesth Analg* 2011; **113:** 540–44.

11 Schlader ZJ, Simmons SE, Stannard SR, Mundel T. The independent roles of temperature and thermal perception in the control of human thermoregulatory behavior. *Physiol Behav* 2011; **103:** 217–24.

12 Nadel ER, Stolwijk JAJ. Sweat gland response to the efferent thermoregulatory signal. *Arch Sci Physiol* 1973; **27:** A67–77.

13 Hales JRS, Jessen C, Fawcett AA, King RB. Skin AVA and capillary dilatation and constriction induced by local skin heating. *Pflügers Arch* 1985; **404:** 203–07.

14 De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. *Anesthesiology* 2002; **96:** 467–84.

15 Affourtit C, Crichton PG, Parker N, Brand MD. Novel uncoupling proteins. *Novartis Found Symp* 2007; **287:** 70–80.

16 Karlberg P, Moore RE, Oliver TK Jr. Thermogenic and cardiovascular responses of the newborn baby to noradrenaline. *Acta Paediatr Scand* 1965; **54:** 225–38.

17 Kajimura S, Saito M. A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis. *Annu Rev Physiol* 2014; **76:** 225–49.

18 Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 2009; **360:** 1509–17.

19 Astrup A, Bulow J, Madsen J, Christensen NJ. Contribution of BAT and skeletal muscle to thermogenesis induced by ephedrine in man. *Am J Physiol* 1985; **248:** E507–15.

20 Sawka MN, Montain SJ. Fluid and electrolyte supplementation for exercise heat stress. *Am J Clin Nutr* 2000; **72** (2 suppl): 564S–72S.

21 Hensel H. Thermoreception and temperature regulation. London: Academic Press; 1981.

22 Eyolfson DA, Tikuisis P, Xu X, Weseen G, Giesbrecht GG. Measurement and prediction of peak shivering intensity in humans. *Eur J Appl Physiol* 2001; **84:** 100–06.

23 Tikuisis P, Eyolfson DA, Xu X, Giesbrecht GG. Shivering endurance and fatigue during cold water immersion in humans. *Eur J Appl Physiol* 2002; **87:** 50–58.

24 Johnston CE, Bristow GK, Elias DA, Giesbrecht GG. Alcohol lowers the vasoconstriction threshold in humans without affecting core cooling rate during mild cold exposure. *Eur J Appl Physiol Occup Physiol* 1996; **74:** 293–95.

25 Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methlendioxymethamphetamine (MDMA or "Ecstasy"). *Psycholpharmacology (Berl)* 1995; **119:** 247–60.

26 Orhan-Sungur M, Komatsu R, Lenhardt R. Buspirone and dexmedetomidine synergistically reduce the shivering threshold in humans. *Anesthesiology* 2006; **105:** A1224.

27 Xiong J, Kurz A, Sessler DI, et al. Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. *Anesthesiology* 1996; **85:** 240–45.

28 Ozaki M, Sessler DI, Suzuki H, Ozaki K, Tsunoda C, Atarashi K. Nitrous oxide decreases the threshold for vasoconstriction less than sevoflurane or isoflurane. *Anesth Analg* 1995; **80:** 1212–16.

29 Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C. Propofol linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **82:** 1169–80.

30 Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR. Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **83:** 293–99.

31 Bissonnette B, Sessler DI. Thermoregulatory thresholds for vasoconstriction in pediatric patients anesthetized with halothane or halothane and caudal bupivacaine. *Anesthesiology* 1992; **76:** 387–92.

32 Ozaki M, Sessler DI, Suzuki H, Ozaki K, Atarashi K, Negishi C. The threshold for thermoregulatory vasoconstriction during nitrous oxide/sevofluruane anesthesia is reduced in elderly patients. *Anesth Analg* 1997; **84:** 1029–33.

33 Plattner O, Semsroth M, Sessler DI, Papousek A, Klasen C, Wagner O. Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. *Anesthesiology* 1997; **86:** 772–77.

34 Annadata RS, Sessler DI, Tayefeh F, Kurz A, Dechert M. Desflurane slightly increases the sweating threshold, but produces marked, non-linear decreases in the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **83:** 1205–11.

35 Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1997; **87:** 835–41.

36 Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K. Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans. *Anesthesiology* 1995; **83:** 1212–19.

37 Ikeda T, Kim J-S, Sessler DI, Negishi C, Turakhia M, Jeffrey R. Isoflurane alters shivering patterns and reduces maximum shivering intensity. *Anesthesiology* 1998; **88:** 866–73.

38 Ikeda T, Sessler DI, Tayefeh F, et al. Meperidine and alfentanil do not reduce the gain or maximum intensity of shivering. *Anesthesiology* 1998; **88:** 858–65.

39 Kurz A, Sessler DI, Annadata R, Dechert M, Christensen R. Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; **81:** 393–98.

40 Lopez M, Ozaki M, Sessler DI, Valdes M. Physiological responses to hyperthermia during epidural anesthesia and combined epidural/enflurane anesthesia in women. *Anesthesiology* 1993; **78:** 1046–54.

41 Cornett PM, Matta JA, Ahern GP. General anesthetics sensitize the capsaicin receptor transient receptor potential V1. *Mol Pharmacol* 2008; **74:** 1261–68.

42 Caterina MJ. Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am J Physiol Regul Integr Comp Physiol* 2007; **292:** R64–76.

43 Glosten B, Sessler DI, Faure EAM, Sten R, Thisted RA, Karl L. Central temperature changes are poorly perceived during epidural anesthesia. *Anesthesiology* 1992; **77:** 10–16.

44 Joris J, Ozaki M, Sessler DI, et al. Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. *Anesthesiology* 1994; **80:** 268–77.

45 Leslie K, Sessler DI. Reduction in the shivering threshold is proportional to spinal block height. *Anesthesiology* 1996; **84:** 1327–31.

46 Doufas AG, Morioka N, Maghoub AN, Mascha E, Sessler DI. Lower-body warming mimics the normal epidural-induced reduction in the shivering threshold. *Anesth Analg* 2008; **106:** 252–56.

47 Kim J-S, Ikeda T, Sessler D, Turakhia M, Jeffrey R. Epidural anesthesia reduces the gain and maximum intensity of shivering. *Anesthesiology* 1998; **88:** 851–57.

48 Sessler DI. Temperature monitoring and perioperative thermoregulation. *Anesthesiology* 2008; **109:** 318–38.

49 Duff GW, Durum SK. Fever and immunoregulation: hyperthermia, interleukins 1 and 2, and T-cell proliferation. *Yale J Biol Med* 1982; **55:** 437–42.

50 Dinarello CA, Bemheim HA, Duff GW, et al. Mechanisms of fever induced by recombinant human interferon. *J Clin Invest* 1984; **74:** 906–13.

51 Blatteis CM, Sehic E, Li S. Pyrogen sensing and signaling: old views and new concepts. *Clin Infect Dis* 2000; **31** (suppl 5)**:** S168–77.

52 Rosenberg H. Overview of drug induced hyperthermic syndromes other than MH. *The Communicator* 2011. Sherburne, NY: Malignant Hyperthermia Association.

53 Negishi C, Lenhardt R, Sessler DI, et al. Desflurane reduces the febrile response to administration of interleukin-2. *Anesthesiology* 1998; **88:** 1162–69.

54 Negishi C, Kim J-S, Lenhardt R, et al. Alfentanil reduces the frebrile response to interleukin-2 in humans. *Crit Care Med* 2000; **28:** 1295–300.

55 Lenhardt R, Negishi C, Sessler DI, et al. The effects of physical treatment on induced fever in humans. *Am J Med* 1999; **106:** 550–55.

56 Mayer S, Commichau C, Scarmeas N, Presciutti M, Bates J, Copeland D. Clinical trial of an air-circulating cooling blanket for fever control in critically ill neurologic patients. *Neurology* 2001; **56:** 292–98.

57 Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surg Infect (Larchmt)* 2005; **6:** 369–75.

58 Kett DH, Breitmeyer JB, Ang R, Royal MA. A randomized study of the efficacy and safety of intravenous acetaminophen vs. intravenous placebo for the treatment of fever. *Clin Pharmacol Ther* 2011; **90:** 32–39.

59 Kasner SE, Wein T, Piriyawat P, et al. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke* 2002; **33:** 130–34.

60 Davatelis G, Wolpe SD, Sherry B, Dayer JM, Chicheportiche R, Cerami A. Macrophage inflammatory protein-1: A prostaglandin-independent endogenous pyrogen. *Science* 1989; **243:** 1066–68.

61 Sessler DI, Schroeder M, Merrifield B, Matsukawa T, Cheng C. Optimal duration and temperature of pre-warming. *Anesthesiology* 1995; **82:** 674–81.

62 Matsukawa T, Sessler DI, Sessler AM, et al. Heat flow and distribution during induction of general anesthesia. *Anesthesiology* 1995; **82:** 662–73.

63 Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia. *Anesthesiology* 1995; **83:** 961–67.

64 Kurz A, Sessler DI, Christensen R, Dechert M. Heat balance and distribution during the core-temperature plateau in anesthetized humans. *Anesthesiology* 1995; **83:** 491–99.

65 Sessler DI. Perioperative heat balance. *Anesthesiology* 2000; **92:** 578–96.

66 Valeri CR, Khabbaz K, Khuri SF, et al. Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. *J Thorac Cardiovasc Surg* 1992; **104:** 108–16.

67 Reed L, Johnston TD, Hudson JD, Fischer RP. The disparity between hypothermic coagulopathy and clotting studies. *J Trauma* 1992; **33:** 465–70.

68 Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement: a meta-analysis. *Anesthesiology* 2008; **108:** 71–77.

69 Kurz A, Sessler DI, Lenhardt RA, Study of wound infections and temperature group. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. *N Engl J Med* 1996; **334:** 1209–15.

70 Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. *Lancet* 2001; **358:** 876–80.

71 Caldwell JE, Heier T, Wright PMC, et al. Temperature-dependent pharmacokinetics and pharmacodynamics of vecuronium. *Anesthesiology* 2000; **92:** 84–93.

72 Heier T, Caldwell JE. Impact of hypothermia on the response to neuromuscular blocking drugs. *Anesthesiology* 2006; **104:** 1070–80.

73 Leslie K, Sessler DI, Bjorksten AR, Moayeri A. Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. *Anesth Analg* 1995; **80:** 1007–14.

74 Lenhardt R, Marker E, Goll V, et al. Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997; **87:** 1318–23.

75 Horn E-P, Sessler DI, Standl T, et al. Non-thermoregulatory shivering in patients recovering from isoflurane or desflurane anesthesia. *Anesthesiology* 1998; **89:** 878–86.

76 Horn E-P, Schroeder F, Wilhelm S, et al. Postoperative pain facilitates non-thermoregulatory tremor. *Anesthesiology* 1999; **91:** 979–84.

77 Park SM, Mangat HS, Berger K, Rosengart AJ. Efficacy spectrum of antishivering medications: meta-analysis of randomized controlled trials. *Crit Care Med* 2012; **40:** 3070–82.

78 Horn E-P, Standl T, Sessler DI, von Knobelsdorff G, Büchs C, Schulte am Esch J. Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. *Anesthesiology* 1998; **88:** 108–13.

79 Kim YS, Kim YI, Seo KH, Kang HR. Optimal dose of prophylactic dexmedetomidine for preventing postoperative shivering. *Int J Med Sci* 2013; **10:** 1327–32.

80 Wadhwa A, Sengupta P, Durrani J, et al. Magnesium sulphate only slightly reduces the shivering threshold in humans. *Br J Anaesth* 2005; **94:** 756–62.

81 Komatsu R, Sengupta P, Cherynak G, et al. Doxapram only slightly reduces the shivering threshold in healthy volunteers. *Anesth Analg* 2005; **101:** 1368–73.

82 Komatsu R, Orhan-Sungur M, In J, et al. Ondansetron does not reduce the shivering threshold in healthy volunteers. *Br J Anaesth* 2006; **96:** 732–37.

83 The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Investigators. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; **120:** 564–78.

84 Frank SM, Higgins MS, Breslow MJ, et al. The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. *Anesthesiology* 1995; **82:** 83–93.

85 Greif R, Laciny S, Rajek A, Doufas AG, Sessler DI. Blood pressure response to thermoregulatory vasoconstriction during isoflurane and desflurane anesthesia. *Acta Anaesthesiol Scand* 2003; **47:** 847–52.

86 Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. *JAMA* 1997; **277:** 1127–34.

87 Carli F, Emery PW, Freemantle CAJ. Effect of peroperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. *Br J Anaesth* 1989; **63:** 276–82.

88 Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology* 1991; **74:** 815–19.

89 Frank SM, Higgins MS, Fleisher LA, Sitzmann JV, Raff H, Breslow MJ. Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. *Am J Physiol* 1997; **272:** R557–62.

90 Kurz A, Sessler DI, Narzt E, Bakar A, Lenhardt R, Huemer G. Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. *J Clin Anesth* 1995; **7:** 359–66.

91 Sun Z, Honar H, Sessler DI, et al. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. *Anesthesiology* 2015; **122:** 276–85.

92 Sessler DI, Schroeder M. Heat loss in humans covered with cotton hospital blankets. *Anesth Analg* 1993; **77:** 73–77.

93 Yoo HS, Park SW, Yi JW, Kwon MI, Rhee YG. The effect of forced-air warming during arthroscopic shoulder surgery with general anesthesia. *Arthroscopy* 2009; **25:** 510–14.

94 Hasegawa K, Negishi C, Nakagawa F, Ozaki M. Core temperatures during major abdominal surgery in patients warmed with new circulating-water garment, forced-air warming, or carbon-fiber resistive-heating system. *J Anesth* 2012; **26:** 168–73.

95 De Witte JL, Demeyer C, Vandemaele E. Resistive-heating or forced-air warming for the prevention of redistribution hypothermia. *Anesth Analg* 2010; **110:** 829–33.

96 Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology* 2001; **95:** 531–43.

97 NICE. Inadvertent perioperative hypothermia. http://www.nice.org.uk/guidance/cg65/resources/guidance-inadvertent-perioperative-hypothermia-pdf (accessed Sept 20, 2015).

98 Lenhardt R, Sessler DI. Estimation of mean body temperature from mean skin and core temperature. *Anesthesiology* 2006; **105:** 1117–21.

99 Langham GE, Maheshwari A, Contrera K, You J, Mascha E, Sessler DI. Noninvasive temperature monitoring in postanesthesia care units. *Anesthesiology* 2009; **111:** 90–96.

100 Ikeda T, Sessler DI, Marder D, Xiong J. The influence of thermoregulatory vasomotion and ambient temperature variation on the accuracy of core-temperature estimates by cutaneous liquid-crystal thermometers. *Anesthesiology* 1997; **86:** 603–12.

101 Iaizzo PA, Kehler CH, Zink RS, Belani kg, Sessler DI. Thermal response in acute porcine malignant hyperthermia. *Anesth Analg* 1996; **82:** 803–09.

102 Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007–2012: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesth Analg* 2014; **119:** 1359–66.