British Journal of Anaesthesia **84** (**5**): 615–28 (2000)

BJA

REVIEW ARTICLE

Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering

D. J. Buggy[1*] and A. W. A. Crossley[2]

[1]University Department of Anaesthesia, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK
[2]Department of Anaesthesia, Southern Derbyshire Acute Hospitals Trust, Derby, UK
**Corresponding author: e-mail:dbuggy@talk21.com*

Br J Anaesth 2000; **84**: 615–28

Keywords: complications, hypothermia; complications, shivering

The maintenance of normothermia is an important function of the autonomic nervous system in homeothermic mammals such as man, as cellular and tissue dysfunction become evident at even minor deviations from normal core body temperature.[48 53 113] In man, core temperature is normally maintained within narrow limits of 36.5–37.5°C,[48] even in the presence of an adverse environmental temperature, by a combination of behavioural and physiological responses. Anaesthesia abolishes behavioural mechanisms and has the potential to disrupt the physiological mechanisms of thermoregulation. Adverse postoperative outcomes, including wound infection, increased surgical bleeding and morbid cardiac events are being associated with mild perioperative hypothermia (33.0–36.4°C).[21 22 26 42–44 52 74 80 84 85 90 109] There is in turn, increased interest in its prevention and treatment, using physical and pharmacological therapy. Hyperthermia or fever, rather than hypothermia, is a more common problem in critically ill patients in intensive care units and has been the subject of a recent editorial.[19] In this review, we concentrate on the mild, inadvertent hypothermia which frequently accompanies clinical anaesthesia.

The strict physiological definition of hypothermia is core temperature greater than one standard deviation (SD) below the mean core temperature for that mammal, under resting conditions in a thermoneutral environment.[10] Studies on healthy, human volunteers have shown that normal human core temperature can range from 36.5 to 37.5°C, with mean values consistently 36.9–37.0 (0.2–0.5)°C.[75 79 82 98] Core hypothermia may thus be said to commence at 36.4°C, but the lower threshold at which mild hypothermia becomes moderate hypothermia is less clearly defined. We have taken the clinical anaesthetist's working definition of mild hypothermia as 33.0–36.4°C, the approximate temperature at which organ dysfunction may begin to develop.[53 113]

Physiology

Thermoregulation is achieved by a physiological control system consisting of peripheral and central thermoreceptors, an integrating control centre and efferent response systems which take compensatory action.[113] Afferent thermal input comes from anatomically distinct cold and warmth receptors, which may be peripheral or central.[53] The central control mechanism, situated in the hypothalamus, determines mean body temperature by integrating thermal signals from peripheral and core structures, and comparing mean body temperature with a pre-determined 'set-point' temperature.[48] In man, the efferent response to effect change in body heat content as required is by behavioural and autonomic means. The latter involves control of cutaneous vascular smooth muscle tone, shivering and non-shivering thermogenesis when increased heat production is indicated, and sweating when heat loss is indicated.[86] Behavioural responses are of importance in both warm and cold challenges, particularly the latter, where in man they are quantitatively more important than the autonomic mechanisms (Fig. 1).

Afferent thermal signals

Much of our knowledge of the structures of the thermoregulatory system has been gleaned from animal studies. The afferent thermal input may be central or peripheral. Thermally sensitive receptors located in the skin and mucous membranes mediate thermal sensation and contribute to thermoregulatory reflexes. Most of these receptors are not necessarily thermospecific and may also mediate mechanical sensation.[48 100] Cold-specific receptors have a peak rate of discharge of impulses at 25–30°C.[48 53] They are innervated by type A-δ nerve fibres. Warm receptors, on the other hand, have maximal discharge rate at 45–50°C and are innervated by type C nerve fibres.[100]

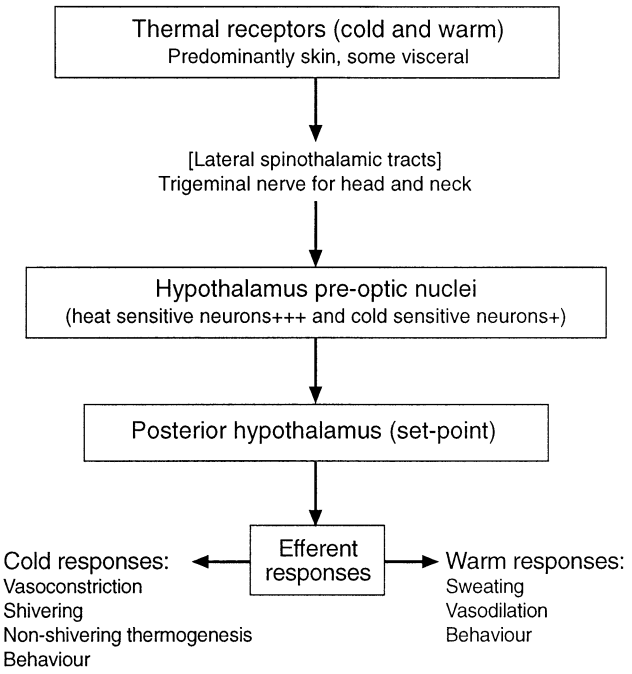

Fig 1 Control of thermoregulation.

Cold receptors respond both to long-term, gradual decreases and to sudden, transient changes in environmental temperature. Transient, violent responses to rates of change in environmental temperature are followed by lasting responses to chronic low levels of skin temperature. This finding was confirmed by Benzinger in a series of experiments in humans subjected to cold water bath stimulation.[7] He studied chemical thermoregulation, which refers to changes in metabolic heat production, usually measured by oxygen consumption. In response to sudden skin temperature reduction by immersion in cold water, oxygen consumption increased acutely and remained elevated, even after the cold stimulus was removed, in response to repeated cold exposure. These findings, together with the observation of 'overshoot inhibition' of oxygen consumption in response to skin surface warming, led to the conclusion that chemical thermoregulation of cold is excited by skin cold receptors and is inhibited by central warm reception.[7 39] Cold receptors in the skin are the major way the body protects itself against cold temperatures, and afferent input from these cold receptors in the skin transmitted to the hypothalamus.[7 8 48]

In addition to peripheral cold receptors, there are central cold receptors of uncertain anatomical location. Their effects are masked by the predominant peripheral influence. Metabolic heat production at warm skin temperatures increases when the core is cooled to less than 36°C.[39] Moreover, it has been demonstrated that some hypothalamic neurones increase their rate of discharge with decreasing core temperature,[51] which is consistent with the observation that there may be impaired response to cold after preoptic hypothalamic lesions[131] or injection of central nervous system (CNS) depressant drugs into the anterior hypothalamus.[130] Central cold thermoreception is considerably less important than peripheral cold sensory input, but studies in patients with spinal cord transection have suggested that this central thermoregulatory process becomes active when the core temperature approaches the lower limit of its set-point range and is less sensitive than the peripheral thermoreceptors.[38]

Central integration – the hypothalamus

Much of the knowledge about the temperature-regulating structures of the hypothalamus has been derived from animal models. The afferent thermal information mechanisms described feed back to temperature-regulating centres in the hypothalamus (Fig. 1). The anterior hypothalamus conducts the integration of afferent thermal information, whereas the posterior hypothalamus controls the descending pathways to effectors.[53] Experiments in animals using thermode technology, whereby a needle-like structure may be placed in minute areas of the brain and its temperature varied by changing the temperature of water passing concentrically within it, have been influential in determining the role of specific brain areas.[13 39 67] The pre-optic area of the hypothalamus contains temperature-sensitive and temperature-insensitive neurones. The former may be subdivided into heat-sensitive and cold-sensitive neurones. The heat-sensitive neurones, which predominate by four to one,[11] increase their discharge rate in response to increased local heat and this activates heat loss mechanisms. Cold-sensitive neurones, conversely, increase their rate of discharge in response to cooling of the pre-optic area of the hypothalamus.[12 14] Neurones sensitive to local thermal stimuli also exist in the posterior hypothalamus, reticular formation and medulla, and spinal cord.[36 65 97]

The posterior hypothalamus integrates cold afferent signals from the periphery with heat-sensitive stimulation from the pre-optic area of the hypothalamus and instigates effector responses. Detection of cold differs from detection of heat, in that it relies on afferent impulses from cutaneous cold receptors,[7 104] rather than reduced discharge rates of the heat-sensitive neurones in the preoptic area.[68] By the time the core body temperature has fallen 0.5°C below normal, the preoptic neurones have become completely inactive so that their signal level cannot be decreased any further. Rather, detection of cold relies on cutaneous cold receptors.[7 104] Although the skin contains both cold and warm receptors, there are 10 times as many cold receptors as warm receptors.[53 104]

Human studies have confirmed that autonomic thermoregulation is dominated by four neural mechanisms: central detection of warmth; peripheral detection of cold; central warm-inhibition of the metabolic response to cold; and finally, inhibition of thermoregulatory sweating by cooling of the skin. The last of these is an antihomeostatic mechanism, which serves to prevent soaking of the skin during strenuous exercise in cool environments.[7 8] In

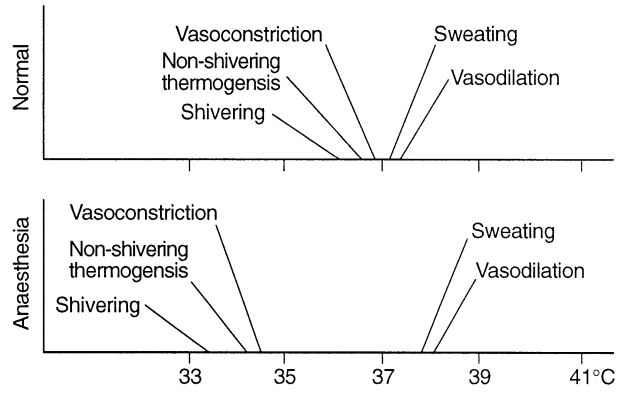

Fig 2 Activation of thermoregulatory effector responses is triggered at specific temperatures for a given individual ('threshold temperature'). Note that under general anaesthesia, the threshold temperatures for activation of cold effector responses (including vasoconstriction and shivering) are 'decreased', whereas those for activation of warm responses (including sweating and vasodilation) are 'increased'. Thus, the narrow range of temperature between the vasoconstriction and sweating thresholds (normally ~0.4°C) is widened during general anaesthesia to ~4.0°C. These data are derived from healthy, fasting human volunteers, with ambient temperature ~23°C and relative humidity 40%. Reproduced, with permission, from Ref. 113.

humans, the 'set-point' temperature may be defined as the narrow temperature range (typically 36.7–37.1°C) across which there is no effector response.[7 113] The set-point has variously been termed a 'thermoneutral zone' or 'inter-threshold range', and is unique to humans. Most mammals are better insulated (usually by fur) than man and use variation in heat production to achieve thermal balance.[53] The limits of this narrow range of temperature are the thresholds at which cold or warm responses are instigated. It is normally no more than 0.4°C, but may be increased to as much as 4.0°C during general anaesthesia in human volunteers (Fig. 2).[113–117] Human studies have also demonstrated a diurnal variation of the set-point, varying from approximately 36.2°C during sleep and in the early morning, to as much as 1°C higher in the evening (6–11 pm). Females have a higher set-point temperature during the luteal phase of the menstrual cycle by ~1°C.[50 53] Rabbit studies have shown that pyrogens may alter the set-point, increasing its triggering temperature by suppressing the activity of warm-responsive neurones, an effect which is reversed by aspirin.[18] Intracranial pathology, such as a space-occupying lesion and dehydration, may also cause an increase in set-point temperature by an unknown mechanism acting upon the temperature-sensitive hypothalamic neurones.[76] The effect of anaesthesia and drugs on thermoregulation and its effector mechanisms is discussed later.

Effector responses

The thermoregulatory responses are characterized by: (i) altered behaviour, quantitatively the most effective mechanism; (ii) a vasomotor response, consisting of vasoconstriction and piloerection in response to cold, and vasodilation and sweating in response to heat; and (iii) shivering and increased metabolic rate.

In the conscious individual, behaviour modification is more powerful than the autonomic mechanisms of regulating body temperature. When the hypothalamic thermostat indicates an excessively cool body temperature, impulses pass from the hypothalamus to the cerebral cortex to give the individual the sensation of feeling cold. The result is modified behaviour, such as increased motor activity, moving to warmer surroundings or adding additional clothing. The control of behavioural responses to cold is based largely on cutaneous thermal signals (see above).[142]

While the precision of the autonomic control of thermoregulation is very high, the power of these mechanisms is limited to less than the equivalent of four basal metabolic rates on either side of the tightly-controlled set-point.[8] Once the set-point temperature range, typically 36.7–37.1°C, has been breached, autonomic effector responses are activated. Each of the specific responses has a characteristic threshold (activation at a specific temperature), gain (rate of response increase as deviation from normal increases) and maximum response intensity.

Benzinger demonstrated that the response to a central cold challenge (e.g. by asking volunteers to consume 500 g ice in a cool environment, 12°C) consisted of a dramatic increase in metabolic rate, which was detected by an increase in oxygen consumption. Moreover, when a subject with a low core temperature (36.1°C) was passively lowered into a 28°C bath, in order to provide a skin cold challenge, metabolic rate also increased ~ 3-fold.[7] In order to understand the interaction of central warm reception and peripheral cold reception, large, independent variations of skin temperatures from 12 to 38°C and tympanic core temperatures from 36 to 38°C were studied in terms of oxygen consumption and sweating rates. The subjects were healthy, naked young men. The values were then plotted on a graph of core temperature versus oxygen consumption (Figs 3 and 4). At first, there seemed no logical interpretation, but when skin isotherms were drawn, graphing core temperature versus oxygen consumption at a given skin temperature, the thermoregulatory response to cold was clarified. In Fig. 3, as the core temperature increases from cold levels (36.6°C) towards the set-point (in this subject, 37.1°C), oxygen consumption and metabolic endogenous heat production decrease at all skin temperatures, but at cold skin temperatures (e.g. 20°C), metabolic heat production continues until the core temperature is warmer than would have been the case if the skin temperature had been 30°C. Once the set-point core temperature is reached, basal metabolic heat production applies, assuming the subject remains at rest. The right-hand portion of Fig. 3 also indicates that as the core temperature increases above the set-point, heat loss mechanisms are strongly activated, as seen in the increased rate of heat loss from evaporation of sweat.[7] Conversely, the effect of increasing skin temperature

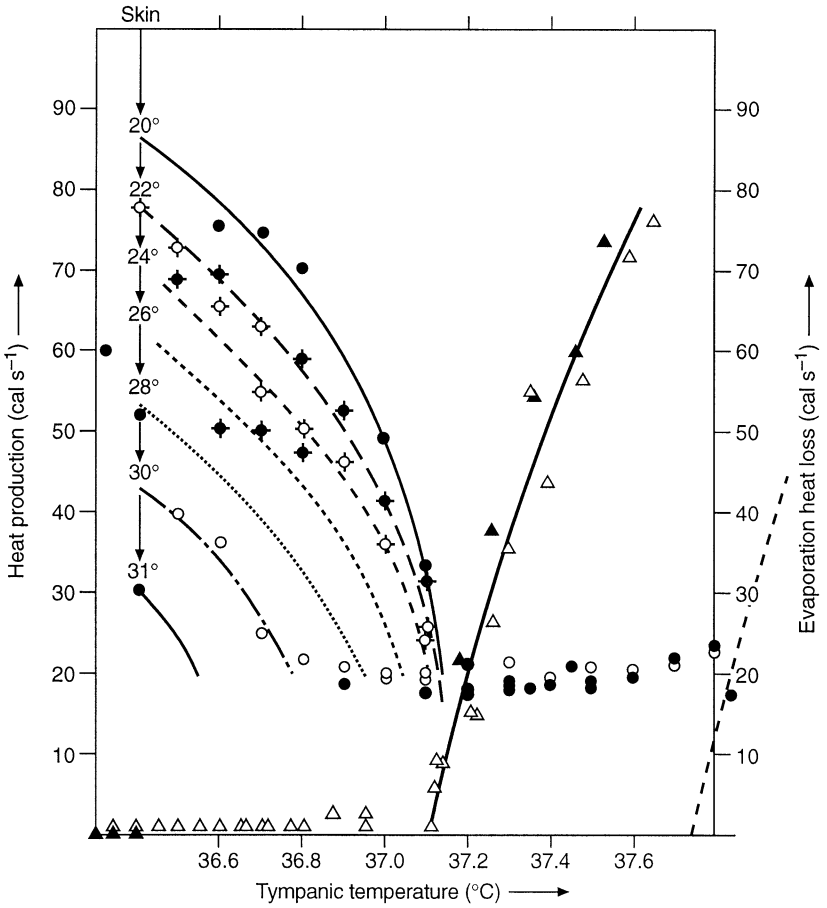

Fig 3 Effect of core temperature on metabolic heat production at different skin temperature isotherms. Note that when skin temperature is relatively cold (20°C), metabolic heat production remains high until the core temperature is >37°C. Data derived from healthy human volunteers. Reproduced, with permission, from Ref. 7.

on metabolic heat production at different core temperature isotherms is shown in Fig. 4.

Shivering and non-shivering thermogenesis

A motor centre for shivering exists adjacent to the centre in the posterior hypothalamus on which the impulses from cold receptors impinge. It is normally inhibited by impulses from the preoptic heat-sensitive area in the anterior hypothalamus, but when the cold impulses exceed the rate at which the former may be received, this motor centre for shivering becomes activated by 'spill-over' of signals and sends impulses bilaterally into the anterior motor neurones of the spinal cord. Initially, this increases the tone of skeletal muscles throughout the body, but when this muscle tone rises above a certain level shivering is observed. This is achieved by increasing the sensitivity of the skeletal muscle stretch reflex.[48 50 53] Two patterns of muscular activity, seen in electromyography studies, contribute to the phenomenon of post-anaesthetic shivering in humans, and are discussed below.[129] While post-anaesthetic shivering may aggravate hypoxaemia,[4] recent work in a rabbit model has suggested that mild hypoxaemia may actually inhibit shivering, by reducing the shivering threshold by more than 1°C.[66]

The elicitation of non-shivering thermogenesis by thermoregulatory noradrenaline release is an important effector mechanism in increasing heat production particularly in neonates.[32] These hormonal mechanisms are particularly important in long-term adaptation to cold. Non-shivering thermogenesis occurs mainly in brown adipose tissue (BAT). This subtype of adipose tissue contains large numbers of mitochondria in its cells and these are supplied by a strong sympathetic nervous system (SNS) innervation. When sympathetic stimulation occurs, oxidative metabolism of the mitochondria is stimulated but is uncoupled to phosphorylation, so that heat is produced instead of generating the metabolic fuel, adenosine triphosphate (ATP). In human adults, the amount of BAT is small and non-shivering thermogenesis increases the rate of heat production by less than 10–15%, in contrast to infants, where it can double heat production.[32] The sympathetic response to mild intraoperative hypothermia and non-shivering thermogenesis are abolished by fentanyl-propofol anaesthesia in infants.[101] An audit of post-anaesthetic shivering in a dedicated paediatric hospital found an overall incidence of shivering of 14% with older age (>6 yr), administration of atropine and intraoperative hypothermia being significantly predictive of shivering.[88]

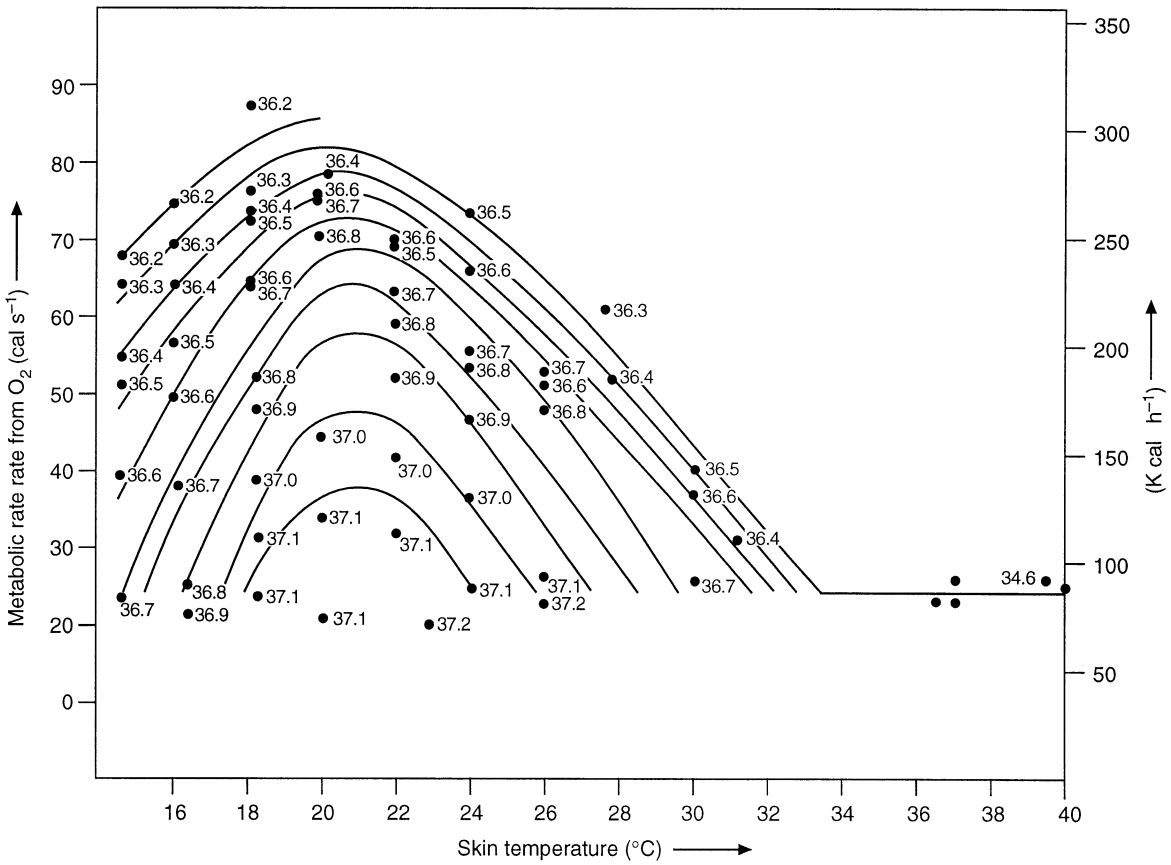

Fig 4 Effect of skin temperature on metabolic heat production at different core temperature isotherms. Note that when the core temperature is relatively cold (36.3°C), metabolic heat production remains high until the skin temperature is >32°C. Data derived from healthy human volunteers. Reproduced, with permission, from Ref. 7.

Heat balance

Heat is a form of energy and temperature is a measure of the amount of heat in a body. Heat balance refers to the total amount of heat in the body, and is increased by metabolic heat production and reduced by evaporation of sweat. Radiation, conduction and convection may increase or decrease the body heat content, depending on environmental circumstances. For example, if ambient temperature is greater than body temperature, radiation will increase body heat content, while the reverse will occur when ambient temperature is less than body temperature.[48] Heat gain processes may be *obligatory*, that is they occur without reference to thermoregulation; or *facultative*, that is they can be manipulated by thermoregulatory mechanisms to restore heat balance. Obligatory heat gain necessarily includes basal metabolic rate (BMR). This is the energy cost of maintaining normal homeostasis within the body and is approximately 40 kcal m^{-2} h^{-1}.[53] It is increased in childhood, in the presence of sympathetic nervous system stimulation by fever, and by hormones such as thyroxine, androgen and growth hormone. It declines with age and is reduced during sleep and malnutrition. Facultative heat gain includes: physical exercise, which if strenuous can increase heat production to 20 times BMR; shivering, which can increase it sixfold above BMR;[53] and non-shivering thermogenesis, which is particularly important in the neonate, but not in adults.[32] Digestion of foods, especially proteins, also has a thermogenic effect.[110–112]

Heat loss at rest is predominantly (75%) by conduction, convection and radiation, with convection being the most important. Convective heat loss occurs when the layer of air next to the skin moves or is disturbed, thereby removing its insulative properties. Radiative heat loss is proportional to the fourth power of the temperature difference between the patient and the ambient environment.[113] The remaining 25% of heat loss at rest is evaporation of insensible water, principally evaporation from the respiratory tract. Sweating involves the active secretion of water on the skin, and because the specific latent heat of vaporization of water is 0.58 Cal g^{-1}, its evaporation can dissipate large amounts of heat, up to 20 times BMR.[48]

Inadvertent hypothermia is by far the most common perioperative thermal abnormality seen, and it results from exposure to a cold environment in a context of impaired thermoregulatory mechanisms.[23] Patients whose normal core temperature is 37°C are anaesthetized and their skin exposed in an operating theatre with an ambient temperature of 20–25°C. The cooling that results is aggravated by the

use of cold antiseptic solutions which are allowed to evaporate from the skin, or by cool fluids instilled into body cavities and by cool intravenous infusions which increase conductive losses. Air turnover rates in theatre (typically 20 cm s^{-1}) will influence convective heat loss.[113]

Measurement of body heat content cannot be achieved directly. However, it may be derived from the product of mean body temperature, body mass and the specific heat of the body. An estimate of mean body temperature (T_{body}) may be obtained from this equation, derived from calorimetric studies:

$$T_{body} = 0.66\ T_{core} + 0.34\ T_{skin},$$

where T_{core} = core body temperature and T_{skin} = mean skin temperature.[28] The accuracy of this equation relies in turn on the adequacy of mean skin temperature measurement. Different areas of skin may be given a different weighting depending on the amount of body surface area it represents.[40] When a high degree of accuracy is required, the mean skin temperature may be estimated using 10 or more skin measurement sites.[123] However, Ramanathan suggested that four skin measurement sites provide adequate accuracy in this calculation without the inconvenience of using a larger number of sites, and this approach has been used successfully in a clinical setting.[55 107] It has been shown that the choice of site for core temperature measurement and the weighting coefficients used in calculating mean body temperature are more important sources of error than is the calculation of mean skin temperature.[106]

Core temperature can reliably be evaluated at the tympanic membrane, distal oesophagus and pulmonary artery. Intraoperative thermal monitoring may be achieved with infrared thermometry of the tympanum or by thermistors placed in the distal oesophagus. Core temperature may also be estimated with nasopharyngeal, axillary, rectal and bladder temperatures, although rectal temperature lags behind other core sites.[29] Skin surface temperature varies with ambient temperature and with induction of anaesthesia, and is usually also measured with a thermistor, or alternatively with a liquid crystal thermometer.[93 113] Measurement of temperature at the skin surface has been used to estimate the core temperature, by heating the sensor to eliminate the core–surface temperature gradient. Deep tissue temperature monitoring in this way at the sternum and forehead correlate well with distal oesophageal temperature (r^2 = 0.7, mean difference from oesophageal temperature = 0.2°C).[93]

Hypothermia during general anaesthesia follows a distinctive pattern and occurs in three phases: an initial rapid decrease in core temperature of ~1°C over the first hour, followed by a slower linear decrease to 34–35°C, after which point a core temperature plateau or thermal equilibrium is reached, where heat loss to the periphery equals heat gained from core metabolic production.[113] The initial rapid reduction in core temperature is greater than that which would be explained by a lowering of metabolic rate and heat loss, and is in fact attributable to core-to-peripheral redistribution of body heat.[54 94] Mean body temperature and body heat content remain constant during this first hour.[116 119] The subsequent core temperature plateau is largely due to thermoregulatory vasoconstriction, triggered by a core temperature of 33–35°C.[5 117]

Effect of general anaesthesia on thermoregulation

Behavioural thermoregulation is redundant during general anaesthesia, and both general and regional anaesthesia obtund normal temperature control mechanisms. The anaesthetist must thus manage the patient's thermoregulatory control. General anaesthesia causes thermoregulatory impairment characterized by an increase in warm-response thresholds and a decrease in cold-response thresholds, such that the normal interthreshold range (between which no effector response occurs) is increased from ~0.4°C to 4.0°C.[115] Both warm-response and cold-response thresholds are affected (Fig. 2). These values have been derived from human volunteer studies, using tympanic thermometry, with ambient temperature usually around 25°C.

All general anaesthetic agents impair thermoregulatory responses to a similar, but not identical, extent. All the currently used potent inhalation anaesthetic agents decrease the vasoconstriction and shivering thresholds (Table 1).[41 62 75 78 98 116] Isoflurane produces a dose-dependent decrease in the threshold for thermoregulatory vasoconstriction, ~3°C per 1% isoflurane concentration.[132] Isoflurane also reduces the shivering threshold and changes the pattern of shivering to include a more clonic type of muscular activity. The latter involves a change from a linear increase in shivering intensity to bouts of intense, clonic shivering followed by quiescent periods.[62] In addition, isoflurane reduces maximum shivering intensity,[62] but gain is generally preserved during general anaesthesia.[132] Desflurane, however, decreases both the threshold and gain of vasoconstriction, the latter threefold from 2.4 to 0.8 ml min^{-1} per °C.[82] Sevoflurane has been shown to produce a dose-dependent reduction in shivering threshold in rabbits.[49] Similarly, the thresholds of the warm-responses, sweating and vasodilatation are increased by inhalation anaesthesia.[138] Thus the effects of anaesthesia on thermoregulatory responses differ from its effects on the carbon dioxide response curve, which displays both increased threshold and decreased gain.[113] During general anaesthesia the thermoregulatory thresholds are lowered further in elderly patients (60–80 yr) than in younger patients, by as much 1°C.[79]

Recently, a study comparing induction of anaesthesia with either sevoflurane or propofol found greater core hypothermia in patients receiving propofol, even though they were subsequently ventilated on sevoflurane and nitrous oxide. These data suggest that even a brief period

Table 1 Characteristics of the cold effector responses in controls and during anaesthesia. All of these studies were on human subjects. N/A indicates data not clearly available. [a]Gain was calculated from laser Doppler fluorimetry; other data on thermoregulatory gain was calculated from oxygen consumption

	Threshold (°C)	Gain (ml O_2 min^{-1} $°C^{-1}$)	Max response intensity (ml O_2 min^{-1} $°C^{-1}$)
Normal vasoconstriction	36.8±0.4[78] 36.6±0.2[41]	2.4[a 82]	N/A
Vasoconstriction under GA	35.6±0.3[78] 34.6±0.4[116]	0.8[a 82]	N/A
Vasoconstriction with epidural	36.2±0.4[41] 36.5±0.2[98]	N/A	N/A
Control shivering	35.7±0.4[98] 36.7±0.6[75]	−580±186[75]	607±82[75] 706±144[62]
Shivering with GA	34.2±0.8[64]	−1480±750[62]	490±80[62]
Vasoconstriction with spinal	36.7±0.3[98]	N/A	N/A
Shivering with spinal	35.5±0.5[98]	N/A	N/A
Shivering with epidural	35.4±0.5[98] 36.3±0.5[75]	−215±154[75]	412±50[75]

of propofol-induced vasodilation causes significant redistribution hypothermia.[63] Intramuscular midazolam 0.075 mg kg^{-1} produced a dose-dependent reduction in tonic thermoregulatory vasoconstriction, significantly reducing core temperatures, even in the absence of conventional anaesthesia.[91]

The effect of general and regional anaesthesia on effector responses is summarized in Table 1.

Effect of regional anaesthesia on thermoregulation

Epidural and spinal anaesthesia decrease the vasoconstriction and shivering thresholds to a comparable degree,[98] but by a lesser amount, of ~0.6°C, than general anaesthetics when measured above the upper level of the block.[81 98 118] Because local anaesthetics administered to the central neuraxis do not directly interact with the hypothalamic control centres and local anaesthetics given intravenously in doses equivalent to plasma levels after epidural anaesthesia have no thermoregulatory effect,[47] the mechanism of this disturbance during regional anaesthesia is unknown, but is consistent with thermoregulatory impairment caused by the effects of the regional block upon afferent thermal information.[81]

In contrast to general anaesthesia, where the gain of thermoregulatory responses is unchanged, the gain of shivering is reduced by 63% and the maximum intensity by 33% following epidural anaesthesia (Table 1). This occurs because shivering above the block compensates for the inability of muscles below the block to engage in shivering.[75] As with general anaesthesia, core hypothermia (by 0.6–1.5°C) occurs during the first hour or so after epidural anaesthesia, due to core-to-peripheral redistribution of body heat from the epidural-induced vasodilation. However, with prolonged epidural anaesthesia, the degree of core hypothermia was less than after general anaesthesia, because of vasoconstriction above the level of the block.[92]

Shivering during regional anaesthesia is, like that after general anaesthesia, preceded by core hypothermia and vasoconstriction above the level of the block, and in addition, has the same electromyography characteristics as that which occurs after general anaesthesia.[61] With reduced gain and maximum intensity, the shivering which is induced by core hypothermia after regional anaesthesia is usually ineffective in preventing core hypothermia, although it has been reported that after treatment of shivering the core temperature may fall further.[122]

Whether shivering seen during epidural analgesia in labour is due to the temperature of the injectate is unclear. Injection of ice-cold epidural local anaesthetic increases shivering compared with epidural solutions that are prewarmed to 30°C.[102] This result was not repeated in non-pregnant patients, however, where no difference in the incidence of shivering was observed between those given warm or cold epidural injections.[103] Shivering during a regional anaesthetic may be averted by maintaining high ambient temperature,[103] by skin-surface warming with radiant heat,[124] or by using the same drugs that are effective for shivering after general anaesthesia (see below).

Interestingly, core hypothermia during regional anaesthesia may not trigger a sensation of cold.[41] This may reflect the fact that subjective cold perception depends on skin temperature afferent input, and that the cutaneous vasodilatation resulting from regional anaesthesia increases skin temperature, leading to a sensation of warmth although accompanied by thermoregulatory shivering.[118] Awareness of core hypothermia is also impaired by epidural anaesthesia.[41]

After the core-to-peripheral redistribution of body heat with induction of general and regional anaesthesia, subsequent further hypothermia depends on the balance of cutaneous heat loss and rate of heat metabolic heat production.[113] During regional epidural anaesthesia, there are two factors which may accelerate heat loss and prevent the emergence of a core temperature plateau seen after general anaesthesia: firstly, there is reduced vasoconstriction threshold in conjunction with lower limb vasodilation due to the block itself. Hence heat loss continues unabated during epidural anaesthesia despite the activation of the effector mechanisms above the level of the block. This is especially seen where general and epidural anaesthesia are combined.[73]

Secondly, epidural anaesthesia further reduces the vasoconstriction threshold during general anaesthesia and increases the rate of core cooling compared with general anaesthesia alone, because vasoconstriction in the quantitatively important leg compartment is inhibited by the block.[73]

Consequences of mild perioperative hypothermia

In particular circumstances, hypothermia may have a protective effect in terms of reducing basal metabolic rate and with it the risk of tissue hypoxia and ischaemia. The efficacy of mild hypothermia in reducing the cerebral metabolic requirement for oxygen exceeds that of barbiturate coma[133 134] and hence may be indicated in carotid arterial surgery or neurosurgery. Moderate hypothermia is routine practice in many cardiac surgery centres using cardiopulmonary bypass, to minimize the risk of myocardial and cerebral ischaemia. It is generally agreed however that the deleterious consequences of mild hypothermia outweigh the potential benefits,[23] with evidence emerging that hypothermia *per se* is responsible for adverse postoperative outcomes. Hypothermia is associated with shivering and excessive sympathetic nervous system stimulation;[43] metabolic acidosis causing prolonged drug metabolism, particularly of neuromuscular antagonists and propofol;[52 85 95] and delayed recovery from anaesthesia.[84] Platelet activity is impaired,[135] and there is prolongation of the coagulation time and decreased clot formation rate.[37 70] Impaired immune function and delayed wound healing have been demonstrated,[127 136] and hypothermia is associated with both increased breakdown and decreased synthesis of muscle protein.[21 22 24] Perioperative thermal discomfort is often remembered by patients as the worst aspect of their perioperative experience.[120]

The hypothesis that perioperative normothermia increases susceptibility to surgical wound infection and lengthens hospitalization was tested in a prospective, randomized trial.[80] Two hundred patients undergoing colorectal surgery were randomly assigned to a routine intraoperative thermal care group (hypothermia group) and an additional warming group (normothermia group). Wounds were evaluated daily until discharge and they were deemed infected if culture-positive pus was isolated. Nineteen percent (19%) of the hypothermia group compared with 6% of the normothermia patients developed wound infections ($P<0.001$). The duration of the hospital stay was also prolonged in the hypothermia group to 13.5 ± 4.5 *vs* 11.8 ± 4.1 days ($P=0.01$). In the hypothermic group, hypothermia persisted for 4 h postoperatively, and their end-of-surgery core temperatures were 34.7°C compared with 36.6°C in those actively warmed. The initial 3–4 h after bacterial contamination are thought to be crucial in determining whether clinical infection ensues.[27]

In vitro studies suggest that platelet and coagulation function are impaired by hypothermia.[37 70 136] The hypothesis that hypothermia may affect surgical bleeding and allogeneic transfusion requirements was also tested in a prospective, randomized trial.[109] Sixty patients undergoing total hip arthroplasty were randomized to normothermia (final core temperature 36.6°C) or mild hypothermia (35.0°C), as described above.[80] Hypothermic patients lost 2.2(0.5) compared with 1.7(0.3) litres of blood (mean(SD), $P<0.001$). Significantly more blood transfusions were required in the hypothermic group.

A number of studies have suggested that mild hypothermia increases cardiac ischaemia and perioperative mortality. A retrospective study showed that the incidence of myocardial ischaemia postoperatively in a group of patients undergoing vascular surgery was raised from 13% to 36% if the patients had a sublingual temperature less than 35°C at the end of the procedure.[42] A prospective, randomized controlled trial comparing over 300 patients with coronary artery disease who either had routine care (and hence were allowed to develop mild hypothermia) or were actively maintained at normothermia during major, non-cardiac surgery found that maintenance of normothermia was associated with a reduced incidence of angina, myocardial infarction, ventricular tachycardia and cardiac arrest than the mildly hypothermic group.[44]

The thermoregulatory response thresholds are lowered during general anaesthesia by 1°C more in elderly patients (60–80 yr) than in younger patients,[79] making them more vulnerable to the occurrence of hypothermia. Prevention of hypothermia in this age group reduces negative nitrogen balance associated with increased protein breakdown or decreased protein synthesis.[21 22]

Physical, active and passive strategies for avoiding perioperative hypothermia

Preventing redistribution-induced hypothermia may be achieved by skin-surface warming. Redistribution of heat occurs when anaesthetic-induced vasodilatation allows heat to flow from the core to the shell down its concentration gradient, effectively abolishing the shell. Pre-emptive skin surface warming, for example by using a forced air-warming device, does not increase core temperature but increases body heat content, particularly in the legs, and removes the gradient for heat loss via the skin.[58] This approach is rarely used in clinical practice, however, because it requires 1 h of prewarming. A shorter, more aggressive period of warming may result in counterproductive sweating and discomfort.[121]

Passive insulation, including cotton drapes, has been used perioperatively to reduce heat loss to the environment,[116] the surface area covered with passive insulation being the important determinant of its effectiveness.[117] However, warming these passive insulators or adding more layers does not improve heat conservation significantly, and passive warming systems are not likely to be effective in longer, more extensive operations.[120] However, a comparison of two passive warming systems during major hepatopancreatic surgery, one with heat reflective properties, unexpectedly found that both core and skin temperature increased in 40%

of patients in each group. This phenomenon may have been due to endogenous heat stimulation by this particular form of surgery.[33] A further study, comparing the efficacy of passive with active skin surface warming, was undertaken in patients undergoing hip arthroplasty. The forced air-warming system was most effective at maintaining normothermia, in comparison with aluminized foil. The latter reduced skin heat loss only, but was unable to prevent the core hypothermia that resulted from core-to-peripheral heat redistribution.[6] Nonetheless, aluminized metallic foil has been shown to increase skin temperature and decrease post-anaesthetic shivering, even after relatively short general anaesthetics,[17] but not during epidural analgesia for labour.[15]

Because only 10% of metabolic heat production is lost in heating and humidifying inspired gases, this method is relatively ineffective at maintaining normothermia.[59] Heat- and moisture-exchanging filters retain significant amounts of moisture and heat within the respiratory system, but are only half as effective as active mechanisms (and only half as expensive).[9] Ambient temperature determines the rate of heat loss by radiation and convection, and should be >23°C to optimally contribute to maintaining normothermia. However, operating room staff usually find these temperatures uncomfortable. Water mattresses are demonstrably ineffective at preventing heat loss, possibly because relatively little heat is lost from the back.[96] Moreover, decreased local tissue perfusion associated with local temperatures of 40°C may lead to skin necrosis.[96] Conductive losses may be reduced if intravenous fluids are warmed before or during administration.[128]

Forced air-warming systems are undoubtedly the best way to maintain normothermia during long procedures, and are particularly effective when used intraoperatively on vasodilated patients, thereby allowing the heat applied to be rapidly transferred to the core. They increase core temperature both intraoperatively and postoperatively, reducing the incidence of post-anaesthetic shivering and thermal discomfort.[6 45 77]

A novel approach to maintaining perioperative normothermia has recently been proposed, based on the principle of prevention. An intravenous infusion of an amino acid mixture commenced before and continued during anaesthesia was found to stimulate metabolic heat production five-fold, compared with the thermogenic effect of amino acids observed in the unanaesthetized state. This thermogenesis was associated with an increased body temperature[110] which originated predominantly from the extra-splanchnic circulation.[112] However, the increased temperature was achieved not only by increased non-shivering thermogenesis, but also by vasoconstriction, reducing cutaneous heat loss.[110 111] The mechanism for this enhanced thermogenic potential during general anaesthesia is as yet unclear. One hypothesis is that in the unanaesthetized subject, there is central inhibition of oxidative metabolism in response to nutrients when the core temperature exceeds the set-point temperature. General anaesthesia may suppress this inhibitory effect, thereby indirectly allowing a thermogenic effect when an amino acid load is presented to the body.[111 112] This hypothesis is supported by the observation that the thermogenic effect of orally ingested amino acids increases in tetraplegic patients, whose neural connection between the central thermosensors and the periphery are severed.[1] Nonetheless, the combination of increased systemic vascular resistance coupled with the increased myocardial demand from the amino acid-induced thermogenesis may be potentially hazardous in patients at high risk of myocardial ischaemia. The role of such amino acid infusions in these higher-risk patients remains to be established.[23]

Post-anaesthetic shivering

Post-anaesthetic shivering is a common complication of modern anaesthesia, affecting 5–65% of patients after general anaesthesia and 33% of patients during epidural regional anaesthesia.[30] It is usually defined as readily detectable fasciculation or tremor of the face, jaw, head, trunk or extremities lasting longer than 15 s.[139] Apart from the obvious discomfort, post-anaesthetic shivering, like hypothermia, is associated with a number of potentially deleterious sequelae. These include increased oxygen consumption and carbon dioxide production,[26 71] catecholamine release,[26] increased cardiac output, tachycardia and hypertension,[4 119] and raised intraocular pressure.[90] Shivering may also decrease mixed venous oxygen saturation,[74] as well as interfering with monitoring.[34]

Post-anaesthetic shivering is often preceded by core hypothermia and vasoconstriction,[119] but not necessarily so.[30 54 56 137] Close observation of post-anaesthetic shivering, later aided by electromyographic studies, revealed that it is composed of two distinct patterns of muscular activity: a tonic pattern with 4–8 cycles min^{-1}, resembling thermoregulatory shivering and a clonic pattern, 5–7 Hz, consistent with uninhibited spinal reflexes.[108 119 129] An audit of over 2500 postoperative patients indicated that male gender, anticholinergic premedication, mode of ventilatory support and induction agents were risk factors for post-anaesthetic shivering, whilst the intraoperative use of pethidine virtually abolished shivering.[31] The use of propofol reduces the incidence of post-anaesthetic shivering as compared to thiopental.[126] Premedication with the muscarinic antagonists, atropine or glycopyrrolate, predisposes to post-anaesthetic shivering. If one accepts that glycopyrrolate penetrates the blood–brain barrier to a lesser degree than atropine, the efficacy of glycopyrrolate would point to a peripheral mechanism of action, possibly by peripheral vasodilation and increased heat loss prior to the induction of anaesthesia.[3]

Treatment of post-anaesthetic shivering

Post-anaesthetic shivering should not be treated in isolation from perioperative hypothermia. Not all patients who shiver are hypothermic, but many are, and successful treatment of

shivering in this group without concomitant treatment of the hypothermia may result in deepening hypothermia.[69 122] A number of the physical methods of treating hypothermia have been shown to reduce the incidence of shivering, in particular forced-air patient warming systems,[77] and radiant heaters.[46 124] Radiant heaters work without increasing core temperature, perhaps by increasing the afferent warm input from the skin of the head and thorax. The mainstay of treatment of postoperative shivering is, however, pharmacological.

A wide range of drugs, including pethidine, other opioids (fentanyl, alfentanil, sufentanil, buprenorphine), doxapram, methylphenidate, clonidine and ketanserin, have all been reported to be effective in suppressing established shivering, and it would be surprising if all worked on a single part of the thermoregulatory mechanism. Pethidine, in particular, is remarkably effective in treating postoperative shivering,[2 25 57 83 87 89 99 140 141] 25 mg being sufficient when given intravenously to stop shivering in the majority of adults. When given in the presence of high-dose naloxone, which antagonizes both μ and κ opioid receptors, pethidine failed to reduce shivering or oxygen consumption, in contrast to its use in combination with low-dose naloxone,[83] suggesting that pethidine exerts its thermoregulatory effects via κ receptors. Pethidine and alfentanil, while reducing the shivering threshold, have been shown not to reduce the gain or maximum intensity of shivering, suggesting that pethidine's efficacy is due to the reduction in the shivering threshold.[64] However, alfentanil, which also decreases the shivering threshold,[78] is less effective than pethidine in treating post-anaesthetic shivering.[87 140]

As stated above, Solliman and Gillies[129] suggested that post-anaesthetic shivering may be due to differential recovery of the brain and spinal cord from anaesthesia, the latter recovering first, resulting in uninhibited spinal clonic tremor, perceived as shivering. Consistent with this hypothesis, doxapram, a cerebral stimulant commonly used as a respiratory stimulant, has also been shown to be effective against shivering, though not as effective as pethidine.[125 141]

Various drugs whose role is less easy to explain are also effective. Physostigmine, the anticholinesterase agent used for reversal of neuromuscular blockade, has been shown to be effective in preventing the onset of post-anaesthetic shivering.[57] This may explain in part why patients who undergo intermittent positive pressure ventilation during anaesthesia shiver less than those who breathe spontaneously,[31] and may imply that cholinergic pathways are involved in the thermoregulatory mechanisms that lead to shivering. Clonidine reduces the thresholds for both shivering and vasoconstriction; is effective in treating established post-anaesthetic shivering;[35 72] has been shown to be effective in suppressing shivering after extradural analgesia in parturients;[20] and given at induction of anaesthesia, will also prevent post-anaesthetic shivering without influencing core and peripheral temperature distribution.[16] The serotonergic antagonist ketanserin reduces established post-anaesthetic shivering,[72] and ondansetron at induction has recently been shown to prevent it, suggesting a role for serotonergic pathways in thermoregulatory control.[105]

Conclusions

Mild perioperative hypothermia is an extremely common but not trivial consequence of induction of anaesthesia, both general and regional. It results from impairment of the physiological set-point, such that the threshold for activation of thermoregulatory effector mechanisms (vasoconstriction and shivering) is reduced to much colder temperatures than would be tolerated in the conscious state. Although regional anaesthesia reduces these thresholds to a lesser extent than general anaesthesia, it more commonly reduces the gain and maximum intensity of the effector responses. Vasodilation induced by anaesthetic agents results in a core-to-peripheral redistribution of body heat, with initial, rapid core hypothermia, followed by a gradual, more linear further decrease in core temperature as heat is lost from the skin, maintaining the core-to-peripheral temperature gradient. When the skin vasoconstriction mechanism finally is activated, skin heat loss decreases and a steady-state situation arises where heat loss is balanced by ongoing metabolic heat production, reduced by only 20% during anaesthesia. Combined general–epidural anaesthesia is a particular risk factor for core hypothermia, as lower limb vasoconstriction, quantitatively the largest part of the peripheral thermal buffer, cannot occur due to the effects of the regional block. On emergence from anaesthesia, normal thresholds are restored, hence hypothermic patients may shiver, which causes a considerable metabolic challenge. The neurotransmitter pathways involved in the control of shivering are complex and involve a number of systems, evidenced by the variety of therapeutic agents that are effective in suppressing it.

The effects of perioperative hypothermia are almost exclusively undesirable. Prevention of perioperative hypothermia and post-anaesthetic shivering, which should be considered and managed as two components of the same syndrome, demonstrably improves the outcome in terms of reduced cardiac morbidity and blood loss, improved wound healing and shorter hospital stay. The known effects of hypothermia on drug metabolism and coagulation are also obviated and studies are indicated to establish the role of perioperative thermoregulation on postoperative myocardial ischaemia. Core temperature monitoring, accompanied by passive and active methods to maintain normothermia, should be part of routine intraoperative monitoring. This is especially so for patients at high risk of perioperative hypothermia, particularly patients undergoing body-cavity surgery, surgery greater than 1 h duration, children, the elderly and cases where combined general–epidural anaesthesia is being conducted. Wider awareness of the benefits of maintaining normothermia perioperatively has the potential to improve the quality of patient care and shorten hospital stay.

References

1 Aksnes AK, Brundin T, Hjeltnes N, Maehlum S, Wahren J. Meal-induced rise in resting energy expenditure in patients with complete cervical spinal cord lesions. *Paraplegia* 1993; **31**: 462–72

2 Alfonsi P, Hongnat JM, Lebrault C, Chauvin M. The effects of pethidine, fentanyl and lignocaine on postanaesthetic shivering. *Anaesthesia* 1995; **50**: 214–7

3 Baxendale BR, Mahajan RP, Crossley AW. Anticholinergic premedication influences the incidence of postoperative shivering. *Br J Anaesth* 1994; **72**: 291–4

4 Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial PO_2 during recovery from anaesthesia. *Br J Anaesth* 1968; **40**: 398–407

5 Belani K, Sessler DI, Sessler AM, *et al*. Leg heat content continues to decrease during the core temperature plateau in humans anesthetized with isoflurane. *Anesthesiology* 1993; **78**: 856–63

6 Bennett J, Ramachandra V, Webster J, Carli F. Prevention of hypothermia during hip surgery: effect of passive compared with active skin surface warming. *Br J Anaesth* 1994; **73**: 180–3

7 Benzinger TH. Heat regulation: homeostasis of central temperature in man. *Physiol Revs* 1969; **49**: 671–759

8 Benzinger TH. Clinical temperature. New physiological basis. *JAMA* 1969; **209**: 1200–6

9 Bissonnette B, Sessler DI, LaFlamme P. Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. *Anesth Analg* 1989; **69**: 192–6

10 Bligh J, Johnson KG. Glossary of terms for thermal physiology. *J Appl Physiol (Lond)* 1973; 35: 941–61

11 Boulant JA, Bignall KE. Hypothalamic neuronal responses to peripheral and deep-body temperatures. *Am J Physiol* 1973; **225**: 1371–4

12 Boulant JA, Demieville HN. Responses of thermosensitive preoptic and septal neurons to hippocampal and brain stem stimulation. *J Neurophysiol* 1977; **40**: 1356–68

13 Boulant JA, Gonzalez RR. The effect of skin temperature on the hypothalamic control of heat loss and heat production. *Brain Res* 1977; **120**: 367–72

14 Boulant JA, Hardy JD. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurones. *J Physiol* 1974; **240**: 639–60

15 Buggy D, Gardiner J. The space blanket and shivering during extraural analgesia in labour. *Acta Anesthesiol Scand* 1995; **39**: 551–3

16 Buggy D, Higgins P, Moran C, O'Donovan F, McCarroll M. Clonidine at induction reduces shivering after general anaesthesia. *Can J Anaesth* 1997; **44**: 263–7

17 Buggy D, Hughes N. Pre-emptive use of the space blanket reduces shivering after general anaesthesia. *Br J Anaesth* 1994; **72**: 393–6

18 Cabanac M, Stolwijk JA, Hardy JD. Effect of temperature and pyrogens on single-unit activity in the rabbit's brain stem. *J Appl Physiol* 1968; **24**: 645–52

19 Campbell IT. Thermoregulation in critical illness. *Br J Anaesth* 1997; **78**: 121–2

20 Capogna G, Celleno D. IV clonidine for post-extradural shivering in parturients: a preliminary study. *Br J Anaesth* 1993; **71**: 294–5

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

22 Carli F, Halliday D. Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthetic rate in surgical patients. *Anesthesiology* 1997; **86**: 1033–40

23 Carli F, MacDonald IA. Perioperative inadvertent hypothermia: what do we need to prevent? *Br J Anaesth* 1996; **76**: 601–3

24 Carli F, Webster J, Pearson M, *et al*. Postoperative protein metabolism: effect of nursing elderly patients for 24 h after abdominal surgery in a thermoneutral environment. *Br J Anaesth* 1991; **66**: 292–9

25 Casey WF, Smith CE, Katz JM, O'Loughlin K, Weeks SK. Intravenous meperidine for control of shivering during caesarean section under epidural anaesthesia. *Can J Anaesth* 1988; **35**: 128–33

26 Ciofolo MJ, Clergue F, Devilliers C, Ben Ammar M, Viars, P. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. *Anesthesiology* 1989; **70**: 737–41

27 Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *New Engl J Med* 1992; **326**: 281–6

28 Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD. Computation of mean body temperature from rectal and skin temperature. *J Appl Physiol* 1971; **31**: 484–9

29 Cork RC, Vaughan RW, Humphrey LS. Precision and accuracy of intraoperative temperature monitoring. *Anesth Analg* 1983; **62**: 211–4

30 Crossley AW. Peri-operative shivering. *Anaesthesia* 1992; **47**: 193–5

31 Crossley AW. Six months of shivering in a district general hospital. *Anaesthesia* 1992; **47**: 845–8

32 Dawkins MJ, Scopes JW. Non-shivering thermogenesis and brown adipose tissue in the human new-born infant. *Nature* 1965; **206**: 201–2

33 Deacock S, Holdcroft A. Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties. *Br J Anaesth* 1997; **79**: 766–9

34 Decourcy JG, Eldred C. Artefactual hypotension from shivering. *Anaesthesia* 1989; **44**: 787–8

35 Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI. Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. *Anesthesiology* 1993; **79**: 470–4

36 Dickenson AH. Specific responses of rat raphe neurones to skin temperature. *J Physiol* (*Lond.*) 1977; **273**: 277–93

37 Douning LK, Ramsay MA, Swygert TH, *et al*. Temperature corrected thrombelastography in hypothermic patients. *Anesth Analg* 1995; **81**: 608–11

38 Downey JA, Chiodi HP, Darling RC. Central temperature regulation in the spinal man. *J Appl Physiol* 1967; **22**: 91–4

39 Downey JA, Mottram RF, Pickering GW. The location by regional cooling of central temperature receptors in the conscious rabbit. *J Physiol (Lond)* 1964; **170**: 415–9

40 DuBois D, DuBois EF. The measurement of the surface area of man. *Arch Int Med* 1915; **15**: 868–73

41 Emerick TH, Ozaki M, Sessler DI, Walters K, Schroeder M. Epidural anesthesia increases apparent leg temperature and decreases the shivering threshold. *Anesthesiology* 1994; **81**: 289–98

42 Frank SM, Beattie C, Christopherson R, *et al*. Unintentional hypothermia is associated with postoperative myocardial ischemia. The Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Anesthesiology* 1993; **78**: 468–76

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

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

45 Giesbrecht GG, Ducharme MB, McGuire JP. Comparison of forced-air patient warming systems for perioperative use. *Anesthesiology* 1994; **80**: 671–9

46 Giesecke A, Sharkey A, Murphy M, Rice L, Lipton J. Control of postanesthetic shivering with radiant-heat. *Acta Anesthesiol Scand* 1987; **31**: 28

47 Glosten B, Sessler DI, Ostman LG, Faure EA, Karl L, Thisted RA. Intravenous lidocaine does not cause shivering-like tremor or alter thermoregulation. *Reg Anesth* 1991; **16**: 218–22

48 Guyton AC. Body temperature, temperature regulation and fever. In: Guyton AC, Hall JE, eds. *Textbook of Medical Physiology*, 9th edition. Philadelphia: W.B. Saunders, 1996; 911–22

49 Hanagata K, Matsukawa T, Sessler DI *et al*. Isoflurane and sevoflurane produce a dose-dependent reduction in the shivering threshold in rabbits. *Anesth Analg* 1995; 81: 581–4

50 Hardy JD. Physiology of temperature regulation. *Physiol Rev* 1961; **41**: 521–86

51 Hardy JD, Hellon RF, Sutherland K. Temperature sensitive neurones in the dog's hypothalamus. *J Physiol (Lond)* 1964; **175**: 242–5

52 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**: 815–9

53 Hervey GR. Thermoregulation. In: Emslie-Smith D, Paterson C, Scratcherd T, Read N, eds. *Textbook of Physiology*, 11th edition. Edinburgh: Churchill-Livingstone, 1988; 510–33

54 Holdcroft A, Hall GM. Heat loss during anaesthesia. *Br J Anaesth* 1978; **50**: 157–64

55 Holdcroft A, Hall GM, Cooper GM. Redistribution of body heat during anaesthesia. A comparison of halothane, fentanyl and epidural anaesthesia. *Anaesthesia* 1979; **34**: 758–64

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

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

58 Hynson J, Sessler DI, Moayeri A. The effects of pre-induction warming on temperature and blood pressure during propofol-nitrous oxide anesthesia. *Anesthesiology* 1993; **79**: 219–24

59 Hynson JM, Sessler DI. Intraoperative warming therapies: a comparison of three devices. *J Clin Anesth* 1992; **4**: 194–9

60 Hynson JM, Sessler DI, Belani K, *et al*. Thermoregulatory vasoconstriction during propofol/nitrous oxide anesthesia in humans: threshold and oxyhemoglobin saturation. *Anesth Analg* 1992; **75**: 947–52

61 Hynson JM, Sessler DI, Glosten B, McGuire J. Thermal balance and tremor patterns during epidural anesthesia. *Anesthesiology* 1991; **74**: 680–90

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

63 Ikeda T, Sessler DI, Kikura M, Kazama T, Ikeda K, Sato S. Less core hypothermia when anesthesia is induced with inhaled sevoflurane than with intravenous propofol. *Anesth Analg* 1999; **88**: 921–4

64 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

65 Inoue S, Murakami N. Unit responses in the medulla oblongata of rabbit to changes in local and cutaneous temperature. *J Physiol* (*Lond*.) 1976; **259**: 339–56

66 Iwashita H, Matsukawa T, Ozaki M, Sessler DI, Imamura M, Kumazawa T. Hypoxemia decreases the shivering threshold in rabbits anesthetized with 0.2 minimum alveolar anesthetic concentration isoflurane. *Anesth Analg* 1998; **87**: 1408–11

67 Jacobson FH, Squires RD. Thermoregulatory responses of the cat to preoptic and environmental temperatures. *Am J Physiol* 1970; **218**: 1575–82

68 Jessen C, Feistkorn G. Some characteristics of core temperature signals in the conscious goat. *Am J Physiol* 1984; **247**: R456–64

69 Johnson MD, Sevarino FB, Lema MJ. Cessation of shivering and hypothermia associated with epidural sufentanil. *Anesth Analg* 1989; **68**: 70–1

70 Johnston TD, Chen Y, Reed RL, II. Functional equivalence of hypothermia to specific clotting factor deficiencies. *Trauma* 1994; **37**: 413–7

71 Jones HD, McLaren CAB. Postoperative shivering and hypoxaemia after halothane, nitrous oxide and oxygen anaesthesia. *Br J Anaesth* 1965; **37**: 35–41

72 Joris J, Banache M, Bonnet F, Sessler DI, Lamy M. Clonidine and ketanserin both are effective treatment for postanesthetic shivering. *Anesthesiology* 1993; **79**: 532–9

73 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

74 Kaplan JA, Guffin AV. Shivering and changes in mixed venous oxygen saturation after cardiac surgery. *Anesth Analg* 1985; **64**: 235–9

75 Kim JS, Ikeda T, Sessler DI, Turakhia M, Jeffrey R. Epidural anesthesia reduces the gain and maximum intensity of shivering. *Anesthesiology* 1998; **88**: 851–7

76 Kluger MJ. Temperature regulation, fever, and disease. *Int Rev Physiol* 1979; **20**: 209–51

77 Krenzischek DA, Frank SM, Kelly S. Forced-air warming versus routine thermal care and core temperature measurement sites. *J Postgrad Anesth Nursing* 1995; **10**: 69–78

78 Kurz A, Go JC, Sessler DI, Kaer K, Lanson MD, Bjorketen AR. Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **83**: 293–9

79 Kurz A, Plattner O, Sessler DI, Huemer G, Redl G, Lackner F. The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than in young patients. *Anesthesiology* 1993; **79**: 465–9

80 Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *New Engl J Med* 1996; **334**: 1209–15

81 Kurz A, Sessler DI, Schroeder M, Kurz M. Thermoregulatory response thresholds during spinal anesthesia. *Anesth Analg* 1993; **77**: 721–6

82 Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K. Desflurane reduces the gain of thermoregulatory arteriovenous shunt vasoconstriction in humans. *Anesthesiology* 1995; **83**: 1212–9

83 Kurz M, Belani KG, Sessler DI, Lanson MD. Naloxone, meperidine, and shivering. *Anesthesiology* 1993; **79**: 1193–201

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

85 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

86 Lindahl SG. Sensing cold and producing heat. *Anesthesiology* 1997; **86**: 758–9

87 Lyons B, Carroll M, McDonald NJ. The treatment of postanaesthetic shivering: a double blind comparison between alfentanil and pethidine. *Acta Anesthesiol Scand* 1995; **39**: 979–8

88 Lyons B, Taylor A, Power C, Casey W. Postanaesthetic shivering in children. *Anaesthesia* 1996; **51**: 442–5

89 Macintyre PE, Pavlin EG, Dwersteg JF. Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. *Anesth Analg* 1987; **66**: 751–5

90 Mahajan RP, Grover VK, Sharma SL, Singh H. Intraocular pressure changes during muscular hyperactivity after general anesthesia. *Anesthesiology* 1987; **66**: 419–21

91 Matsukawa T, Hanagata K, Ozaki M, Ivashita H, Koshimizu M, Kumazawa T. I.m. midazolam as premedication produces a concentration-dependent decrease in core temperature in male volunteers. *Br J Anaesth* 1997; **78**: 396–9

92 Matsukawa T, Sessler DI, Christensen R, Ozaki M, Schroeder M. Heat flow and distribution during epidural anesthesia. *Anesthesiology* 1995; **83**: 961–7

93 Matsukawa T, Sessler DI, Ozaki M, *et al*. Comparison of distal oesophageal temperature with 'deep' and tracheal temperatures. *Can J Anaesth* 1997; **44**: 433–8

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

95 Miller RD. Pharmacokinetics of competitive muscle relaxants. *Br J Anaesth* 1982; **54**: 161–7

96 Morris RH, Kumar A. The effect of warming blankets on maintenance of body temperature of the anesthetized, paralyzed adult patient. *Anesthesiology* 1972; **36**: 408–11

97 Nakayama T, Hardy JD. Unit responses in the rabbit's brain stem to changes in brain and cutaneous temperature. *J App Physiol* 1969; **27**: 848–57

98 Ozaki M, Kurz A, Sessler DI, *et al*. Thermoregulatory thresholds during epidural and spinal anesthesia. *Anesthesiology* 1994; **81**: 282–8

99 Pauca AL, Savage RT, Simpson S, Roy RC. Effect of pethidine, fentanyl and morphine on post-operative shivering in man. *Acta Anesthesiol Scand* 1984; **28**: 138–43

100 Pierau FK, Wurster RD. Primary afferent input from cutaneous thermoreceptors. *Fed Proc* 1981; **40**: 2819–24

101 Plattner O, Semsroth M, Sessler DI, *et al*. Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. *Anesthesiology* 1997; **86**: 772–7

102 Ponte J, Collett BJ, Walmsley A. Anaesthetic temperature and shivering in epidural anaesthesia. *Acta Anesthesiol Scand* 1986; **30**: 584–7

103 Ponte J, Sessler DI. Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers. *Br J Anaesth* 1990; **64**: 731–3

104 Poulos DA. Central processing of cutaneous temperature information. *Fed Proc* 1981; **40**: 2825–9

105 Powell RM, Buggy DJ. Ondansetron at induction reduces shivering after general anaesthesia. *Anesth Analg* 2000; **90**: in press

106 Puhakka K, Anttonen H, Niskanen J, Ryhanen P. Calculation of mean skin temperature and changes in body heat content during paediatric anaesthesia. *Br J Anaesth* 1994; **72**: 548–53

107 Ramanathan NL. A new weighting system for mean surface temperature of the human body. *J Appl Physiol* 1964; **19**: 531–3

108 Rosenberg H, Clofine R, Bialik O. Neurologic changes during awakening from anesthesia. *Anesthesiology* 1981; **54**: 125–31

109 Schmied H, Kurz A, Sessler DI, Kozek S, Reiter A. Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. *Lancet*, 1996; **347**: 289–92

110 Sellden E, Branstrom R, Brundin T. Preoperative infusion of amino acids prevents postoperative hypothermia. *Br J Anaesth* 1996; **76**: 227–34

111 Sellden E, Brundin T, Wahren J. Augmented thermic effect of amino acids under general anaesthesia: a mechanism for prevention of anaesthesia-induced hypothermia. *Clin Sci* 1994; **86**: 611–8

112 Sellden E, Branstrom R, Brundin T. Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extra-splanchnic tissues. *Clin Sci* 1996; **91**: 431–9

113 Sessler DI. Temperature monitoring. In: Millar RD, ed. *Anesthesia*. New York: Churchill Livingstone, 1994; 1363–82

114 Sessler DI. Perianesthetic thermoregulation and heat balance in humans. *FASEB J* 1993; **7**: 638–44

115 Sessler DI. Central thermoregulatory inhibition by general anaesthesia. *Anesthesiology* 1991; **75**: 557–9

116 Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T. Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases cutaneous heat loss. *Anesthesiology* 1992; **76**: 670–5

117 Sessler DI, Moayeri A, Stoen R, Glosten B, Hynson J, McGuire J. Thermoregulatory vasoconstriction decreases cutaneous heat loss. *Anesthesiology* 1990; **73**: 656–60

118 Sessler DI, Ponte J. Shivering during epidural anesthesia. *Anesthesiology* 1990; **72**: 816–21

119 Sessler DI, Rubinstein EH, Moayeri A. Physiologic responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991; **75**: 594–610

120 Sessler DI, Schroeder M. Heat loss in humans covered with cotton hospital blankets. *Anesth Analg* 1993; **77**: 73–7

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

122 Sevarino FB, Johnson MD, Lema MJ, Datta S, Ostheimer GW, Naulty JS. The effect of epidural sufentanil on shivering and body temperature in the parturient. *Anesth Analg* 1989; **68**: 530–3

123 Shanks CA. Mean skin temperature during anaesthesia: an assessment of formulae in the supine surgical patient. *Br J Anaesth* 1975; **47**: 871–5

124 Sharkey A, Lipton JM, Murphy MT, Giesecke AH. Inhibition of postanesthetic shivering with radiant heat. *Anesthesiology* 1987; **66**: 249–52

125 Singh P, Dimitriou V, Mahajan RP, Crossley AW. Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71**: 685–8

126 Singh P, Harwood R, Cartwright DP, Crossley AW. A comparison of thiopentone and propofol with respect to the incidence of postoperative shivering. *Anaesthesia* 1994; **49**: 996–8

127 Slotman GJ, Jed EH, Burchard KW. Adverse effects of hypothermia in postoperative patients. *Am J Surg* 1985; **149**: 495–501

128 Smith CE, Gerdes E, Sweda S, *et al*. Warming intravenous fluids reduces perioperative hypothermia in women undergoing ambulatory gynecological surgery. *Anesth Analg* 1998; **87**: 37–41

129 Soliman MG, Gillies DM. Muscular hyperactivity after general anaesthesia. *Can Anaesth Soc J* 1972; **19**: 529–35

130 Squires RD. Thermoregulatory effects of injections of gamma amino butyric acid (GABA) and picrotoxin into medial preoptic region of cats. *Fed Proc* 1967; **26**: 555–9

131 Squires RD, Jacobson FH. Chronic deficits of temperature regulation produced in cats by preoptic lesions. *Am J Physiol* 1968; **214**: 549–60

132 Stoen R, Sessler DI. The thermoregulatory threshold is inversely proportional to isoflurane concentration. *Anesthesiology* 1990; **72**: 822–7

133 Todd MM, Warner DS. A comfortable hypothesis reevaluated. Cerebral metabolic depression and brain protection during ischemia. *Anesthesiology* 1992; **76**: 161–4

134 Vale RJ. Cooling during vascular surgery. *Br J Anaesth* 1972; **44**: 1334

135 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

136 Van Oss CJ, Absolom DR, Moore LL, Park BH, Humbert JR. Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O_2 consumption of human polymorphonuclear leukocytes. *J Reticuloendothelial Soc* 1980; **27**: 561–5

137 Vaughan MS, Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming. *Anesth Analg* 1981; **60**: 746–51

138 Washington DE, Sessler DI, Moayeri A, *et al*. Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. *J Appl Physiol* 1993; **74**: 82–7

139 Webb PJ, James FM III, Wheeler AS. Shivering during epidural analgesia in women in labor. *Anesthesiology* 1981; **55**: 706–7

140 Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; **79**: 541–2

141 Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethidine and doxapram in the treatment of post-anaesthetic shivering. *Anaesthesia* 1997; **52**: 32–6

142 Wyss CR, Brengelmann GL, Johnson JM, Rowell LB, Silverstein D. Altered control of skin blood flow at high skin and core temperatures. *J Appl Physiol* 1975; **38**: 839–45