

Inadvertent intraoperative hypothermia

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Abstract

Inadvertent perioperative hypothermia complicates a large percentage of surgical procedures and is related to multiple factors. Strictly regulated in normal conditions ($\pm 0.2^{\circ}\text{C}$), the core body temperature of an anaesthetised patient may fall by as much as 6°C , while a 2°C decrease is very common. This is due to a combination of anaesthesia-related impairment of the central thermoregulatory control and a cool operating room temperature, which, when superimposed on insufficient insulation and a failure to actively warm the patient, may result in profound temperature disturbances. As a result, prolonged wound healing, increased risk of wound infection, a higher rate of cardiac morbidity, and greater intraoperative blood loss and postoperative blood transfusion requirements may occur. The reasons for this are said to include underlying changes in microcirculation, coagulation, immunology and an increase in the duration of action of most anaesthesia medications. As effective methods have been available for a number of years now, it is currently indicated to maintain intraoperative normothermia in order to minimise procedure-related risk and improve patient comfort.

Key words: intraoperative hypothermia, thermoregulation, adverse effects, general anaesthesia, neuraxial anaesthesia

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Temperature is one of the elements of homeostasis impaired during anaesthesia. The several-decade observations reveal that inadvertent hypothermia is the most common intraoperative complication that can significantly affect many physiological processes and the postoperative course. However, neither hypothermia nor a target temperature range in anaesthetised patients has been explicitly defined. A core body temperature of 36°C was assumed to be the borderline value of hypothermia [1]. Physiologically, the core temperature fluctuates around 37°C and is rarely below 36.5°C [2]. Convincing evidence demonstrates that an intraoperative temperature decrease even by $1.0\text{--}1.4^{\circ}\text{C}$ exerts adverse effects; therefore, the earlier suggestions that intraoperative core temperature should not be lower than 35°C are not fully justified [3].

PHYSIOLOGY OF THERMOREGULATION

The process of thermoregulation consists of peripheral perception, central regulation and efferent responses. In the 60ties of the previous century, it was unequivocally

demonstrated that the skin was not the only tissue capable of activating the process of thermoregulation and that internal tissues and organs were involved in peripheral perception [4]. The afferent signals are transmitted by A fibres (sensation of cold) and unmyelinated C fibres (sensation of heat). The anatomy of the afferent pathway of temperature conduction from the skin has been thoroughly elucidated yet the thermal signal transmission from internal tissues still needs to be clearly defined. However, it is known that thermoreceptors are located in the fibres of visceral nerves and the vagus nerve, widespread in the abdominal cavity. The centre of thermoregulation is situated in the preoptic area of the hypothalamus and receives impulses from the skin and internal organs. The centre is to maintain the body time-adjusted temperature; under normal conditions, it is activated already at very slight deviations from the set temperature ($< 0.2^{\circ}\text{C}$) and the activation threshold changes with time. The functioning of the hypothalamic thermoregulatory centre can be explained based on two basic terms, i.e. a setpoint and an inter-threshold range. These

phenomena are essential for understanding the pathogenesis of intraoperative hypothermia. Under physiological conditions, the core body temperature shows rhythmic changes in both genders (circadian rhythm $\pm 1^\circ\text{C}$) and monthly fluctuations in females ($\pm 0.5^\circ\text{C}$), which corresponds to daily and monthly changes in the setpoint temperature. The inter-threshold range (about 0.2°C) is the acceptable zone of temperatures, within which the mechanisms preventing cooling or overheating are not yet activated [5]. The study findings reveal that many endogenous substances, e.g. noradrenaline, dopamine, acetylcholine, prostaglandin E_1 , neuropeptides and serotonin, are crucial for maintaining the setpoint and inter-threshold range at the stable level; the dominant role of one of them has not been explicitly established. However, there is convincing evidence that the GABAergic system plays a key role in modulating efferent responses to cooling [6, 7].

Monitoring of core temperature is recommended during the majority of general anaesthetic procedures to detect and treat both hypothermia and hyperthermia, including malignant hyperthermia and hyperthermia resulting from other causes, such as complications attributable to transfusions of blood or blood products, infections, haemorrhage to the IV cerebral ventricle. The locations suitable for measurements of body temperature corresponding to core temperature, i.e. the closest one to the temperature of the thermoregulation centre, which are characterised by good dynamics and are technically available include the pulmonary artery, tympanic membrane, distal oesophagus and nasopharynx. Intraoperative measurements using a detector placed in the distal oesophagus appear to be most justified due to low invasiveness of the procedure (as opposed to pulmonary artery cannulation), high accuracy and a minimal risk of complications. Measurements with a detector placed on the tympanic membrane and in the nasopharynx carry high risks of errors associated with the placement technique itself [3, 8].

BODY REACTIONS IN RESPONSE TO COOLING

The man-environment exchange of energy (heat) occurs via four processes: radiation (emission of electromagnetic infrared waves), accounting for the highest daily heat loss of about 60%; conduction, i.e. transfer of heat from the body of higher temperature to the body of lower temperature; convection, i.e. movement of air above the skin or of blood under its surface, which enables continuous warming of fresh air and cooling of blood flowing in the skin; evaporation (mainly undetectable losses of water through the lungs, which account for about 10% of heat loss under normal conditions) [9].

During the evolution, the human body developed several basic protective systems that prevent excessive cooling and overheating.

The mechanisms preventing hypothermia include:

- behavioural (suitable clothes providing good isolation from external factors and staying in the preferably most comfortable ambient temperature);
- peripheral vasoconstriction;
- increased production of heat — shivering thermogenesis (the crucial mechanism to increase the production of heat at sudden temperature changes) and non-shivering thermogenesis (slower heat production activated at longer exposure to a cooling factor).

The mechanisms preventing hyperthermia involve:

- peripheral vasodilation;
- perspiration.

The temperature of external body layers is much more susceptible to environmental factors than the core temperature [10], as under normal conditions the effectiveness of protective behavioural mechanisms is usually sufficient to maintain thermal comfort inside the body. If the above fails, the body placement in the lower temperature surroundings results in cooling of external tissues (skin); this signal is transmitted to the hypothalamus and cerebral cortex, and protective mechanisms are activated. This increases heat production and can occur in all tissues, yet the centrally controlled increase in thermogenesis mainly regards the brown adipose tissue, myocardium and skeletal muscles [11].

Recently, much attention has been paid to brown adipose tissue as a key effector of non-shivering thermogenesis. Located predominantly in the region of the neck, clavicles, around the aorta and kidneys, brown adipose tissue is considered the separate system devoted to processes of thermoregulation, control of energy resources, which also affects the vascular biology. Perivascular adipose tissue, the vessel-supporting tissue (the function similar to that of the connective tissue), which acts paracrinally, shows the characteristics comparable to brown adipose tissue [12].

EFFECT OF GENERAL ANAESTHESIA ON TEMPERATURE FLUCTUATIONS

During general anaesthesia, core temperature of almost all patients decreases by even 3°C [13]. The severity of hypothermia depends of the type and amount of general anaesthetics used, extent of surgery and ambient temperature [14].

A decrease in temperature during anaesthesia is dynamic and follows the defined pattern, i.e. during the first hour of anaesthesia, temperature drops quite rapidly by about $1\text{--}1.5^\circ\text{C}$; during the subsequent 2–3 hours, the reduction is slower to reach finally *plateau* [15]. The causes leading to the aforementioned processes are different at various phases. The initial phase of hypothermia is induced by a decrease in temperature threshold in the hypothalamus, in re-

sponse to which the thermoregulation centre increases the peripheral flow (under normal conditions, the mechanism protecting against overheating) and by direct effects of general anaesthetics on the precapillaries, which substantially increases the external tissue flow causing re-distribution of heat from the central to peripheral compartment without however markedly changing the total amount of body heat. One of the important factors determining the range of core temperature changes during the initial phase of anaesthesia, dependent on heat re-distribution, is the amount of adipose tissue. Re-distribution is more pronounced in slim individuals compared to obese ones, most likely due to a generally low gradient between the core and peripheral temperature in the latter (at good isolation provided by the subcutaneous tissue, heat loss requires a proper blood supply).

During the next hours of anaesthesia (surgery), a further decrease in body temperature is caused by reduced production of heat, usually at increased heat loss. This results from significantly decreased metabolism during general anaesthesia (slowed down cerebral metabolism is likely to be essential) and diminished heat production by skeletal muscles due to reduced work of respiratory muscles during mechanical ventilation. At this stage of anaesthesia, heat from the skin and wound area is lost mainly through radiation and convection and is the main factor determining the development of hypothermia [16]. Therefore, good isolation of the patient and suitable temperature in the operating theatre are pivotal for prevention of heat losses, which has been known for several decades yet surgeons and anaesthesiologists seem still unaware of the issue [14]. A decrease in body temperature is similar to the linear function in time and ends with the onset of the *plateau* phase. This phase develops after several hours of surgery and results from reaching the balance between heat production and its loss. In patients, who are not markedly cooled, the *plateau* phase is achieved passively without the activation of peripheral mechanisms preventing hypothermia whereas in cases of substantial or sudden decreases in core temperature during the linear phase, this phase is achieved thanks to preventing heat escape from the central compartment through peripheral vasoconstriction.

Excessive heat loss related to surgery is partially self-limiting — the lower the body temperature, the slower the heat exchange with the surroundings.

EFFECT OF REGIONAL ANAESTHESIA ON TEMPERATURE FLUCTUATIONS

Regional anaesthesia impairs the control of thermoregulation at the central and peripheral level, predominantly at the latter [17]. It eliminates nerve conduction to the area supplied, which in spinal and epidural anaesthesia involves the substantial part of the body, impairing the mechanisms

preventing cooling of the anaesthetized region. Therefore, during central blocks the unintended body cooling is a common complication, although its characteristics are different from those observed during general anaesthesia. In the anaesthetized area, the effects of sympathetic impulsion maintaining the appropriate vascular tone are less potent, which increases the vascular bed volume. The blood flow in anaesthetized lower limbs increases about fourfold, which mostly results from peripheral re-distribution of blood, hence of heat [18]. The above mechanism of re-distribution is responsible for the initial decrease in core temperature, although to a lesser degree than in general anaesthesia [19, 20] (which is likely to be associated with the relatively constant level of metabolism throughout the regional anaesthesia). Thanks to that, the linear phase of temperature drop starts later and with higher amounts of heat. However, in general anaesthesia the core temperature stabilises after peripheral vasoconstriction whereas in regional the hypothermia deepens, which in long-term procedures and insufficient isolation of the patient's body can lead to substantial cooling [19].

Additionally, it seems that the hypothalamic thermoregulatory centre of thermoregulation interprets the temperature of the anaesthetized area as elevated, which can explain better thermal comfort reported by patients during the first period of regional anaesthesia (or "pleasant warmth" in the anaesthetized area). This reduces the temperature at which preventive mechanisms are activated [21], including muscle shivers, which are rarely effective due to sedatives and their active counteracting during surgery [22, 23]. The combined use of regional and general anaesthesia is a specific situation in which the risk of intraoperative hypothermia additionally increases. The initial cooling associated with re-distribution precedes rapid heat losses in the linear phase, which may be longer and quicker. This partially results from the substantially reduced threshold of vasoconstriction, which occurs later and at lower central temperature [24], but mainly from blocking the peripheral flow reduction in the lower body part [25]. The lack of possible compensation through shivering is also important, which in cases of isolated regional techniques might prevent hypothermia to some extent (at least hypothetically).

CONSEQUENCES OF INTRAOPERATIVE HYPOTHERMIA

Reduced core body temperature is not always an undesirable phenomenon and can be used therapeutically in certain clinical situations. Beneficial impact of reduced temperature has been described during some neurosurgical and cardiac procedures; therapeutic hypothermia is also used in intensive therapy. The ways to induce hypothermia, its values and optimal duration are being researched.

EFFECTS OF HYPOTHERMIA ON PHARMACOKINETICS OF AGENTS USED DURING ANAESTHESIA

The rate of enzymatic reactions at which organism metabolises the chemical compounds administered during anaesthesia can adversely affect the duration of action of all general anaesthetics. Hypothermia has been demonstrated to prolong the action of the majority of non-depolarising relaxants [26, 27, 28, 29] and to affect the pharmacodynamics of depolarising agents (albeit to a lesser degree) [26]. Vecuronium well depicts the relevance of these effects. Its clinical relaxing action doubles following a decrease in core temperature by 2°C. More severe abnormalities are observed in pharmacokinetics than pharmacodynamics of vecuronium, due to markedly prolonged time of plasma clearance and only slightly prolonged time required for the agent to get from the circulation to the neuromuscular junction [29]. According to the researchers, the possibly delayed liver metabolism of vecuronium (at proper liver perfusion) and its reduced renal clearance (at decreased renal perfusion) are the major causes. The hypothermia-related abnormalities are similar for rocuronium but less severe for atracurium. In the case of the latter, a decrease in body temperature by 3°C below the normal value prolongs the relaxation time by about 60% [30, 31]. Interestingly, the sensitivity of the motor plate itself to relaxants seems unchanged in the range of temperatures studied [29, 32].

Moreover, hypothermia alters the characteristics of action of inhalational anaesthetics. At reduced temperatures, their solubility in tissues increases, resulting in increased anaesthetic content in the body at particular equilibrium state. Thus, the minimum alveolar concentration (MAC) slightly decreases, which was demonstrated for isoflurane, halothane and desflurane in animals [33, 34, 35] as well as for isoflurane in children undergoing anaesthesia in hypothermia for cardiac surgeries where MAC decreased by 5.1% per each 1°C of body temperature [36]. The extent of MAC decreases is comparable for all anaesthetics and, interestingly, does not depend on the baseline fat solubility, although improved lipophilicity at reduced temperature baseline fat solubility is responsible for the changes described.

Likewise, plasma concentrations of propofol increase by about 30% at a decrease in body temperature by 3°C by impairing the exchange of the agent between the vascular and peripheral compartments. In this particular case, as opposed to inhalation anaesthetics, the additional factor increasing the plasma level of propofol is decreased liver perfusion during its infusion, with the highest difference in its concentration at hypothermia observed during the first 5 min. of infusion [30].

Opioid analgesics also show prolonged action in hypothermia, which is associated with increased plasma concentrations of fentanyl [37] and remifentanyl [38], on average by 25%, compared to normothermia.

EFFECTS OF HYPOTHERMIA ON THE MYOCARDIUM

Acute coronary incidents are one of the most common causes of complications and deaths in the perioperative period. Although intraoperative hypothermia seems to have no significant effect on the cardiovascular efficiency in young, healthy individuals [39], the incidence of perioperative coronary events in the elderly can increase even threefold at intraoperative hypothermia of 1.4°C [40]. The pathomechanism of this relation has not been fully elucidated; however, two causes are implicated: after the completion of anaesthesia complicated by hypothermia, the plasma concentration of noradrenaline increases even several times, which is associated with unblocking of the thermoregulation centre and activation of the sympathetic mechanism reducing body temperature, i.e. vasoconstriction. This significantly elevates the arterial blood pressure and increases the risk of ventricular tachyarrhythmia. Another cause is shivering, which increases heat production simultaneously substantially increasing oxygen requirements (in young individuals even by 400%), including myocardial requirements, yet to a lesser degree [41]. In the elderly patients administered opioids, postoperative shivering is relatively rare; nevertheless, when the coronary disease coexists this can increase the frequency of cardiac complications. Postoperative shivering is most commonly induced by central hypothermia, although it is also likely to develop in patients with normal body temperature. Such a complication is prevented and treated with μ receptor agonists (alfentanil) and other compounds whose mechanism of action has not been fully explained (clonidine, physostigmine, and magnesium sulphate). Amongst the well-tolerated and easily accessible analgesics of proved beneficial effects are pethidine and tramadol [42]. Moreover, physical warming of patients before the induction of anaesthesia (30 mins–2 h) significantly reduces the incidence of intraoperative hypothermia and postoperative shivering [43].

EFFECTS OF HYPOTHERMIA ON THE RISK OF SURGICAL SITE INFECTION

Surgical wound infections complicate up to 10% of abdominal surgical procedures. Possible adverse effects of hypothermia can result from two mechanisms: reduced peripheral blood flow (vasoconstriction) and impaired immune system. A significant correlation between T lymphocyte-dependent production of immunoglobulins and temperature has been demonstrated, as in the case of non-specific bactericidal activity of neutrophils [44]. The relation largely depends on the availability of oxygen, similarly to proper wound healing. The reduced availability of this substrate can partly explain higher incidence rates of wound infections in intraoperative hypothermia cases and longer hospitalization, even in the absence of infections. The additional causative factors include higher postoperative protein

loss and clotting disturbances, mainly the impaired function of platelets necessary for the initiation of proper healing through platelet plug formation. The above-mentioned disorders lead to even threefold higher incidence of surgical wound infections and substantially reduced reactivity of the immune system in response to infection. According to the study in patients undergoing surgeries due to colon cancers, the changes in question were observed already at core temperature 2°C lower than normal temperature [45].

EFFECTS OF HYPOTHERMIA ON THE CLOTTING SYSTEM

In many cases, proper processes of haemostasis decide about the success of surgery. It is not surprising that clotting disturbances caused by intraoperative hypothermia arouse many emotions amongst clinicians aware of this problem. Reduced temperature affects the clotting process at several stages: it impairs the platelet function, prolongs the prothrombin time and clotting time and can affect fibrinolysis.

The platelet count during hypothermia to 34°C remains generally unchanged, decreasing slightly at lower values of hypothermia whereas platelet activation is impaired already at slight temperature fluctuations. Reduced synthesis of thromboxane B₂ and thrombin, the relevant platelet activators, is most likely the major cause of these disturbances although the ability of platelets to form the platelet plug is not reduced. Otherwise, *in vitro* studies have demonstrated changes in platelet morphology (which can indicate their activation) and enhanced ability to aggregate, most likely caused by facilitated activation of the GP IIb–IIIa receptor during hypothermia, possibly resulting from slowed down hydrolysis of adenosine diphosphate (ADP). This phenomenon can pose a relevant problem during procedures with extracorporeal circulation; therefore, attempts have been made to block it pharmacologically [46, 47].

Hypothermia prolongs the prothrombin time and activated partial thromboplastin time proportionally to the extent of temperature reduction by decreasing the activity of enzymatic processes [48]. The detection of the above changes under clinical conditions is quite difficult as all coagulation tests are carried out in the laboratory at 37°C, which does not reflect the real picture. *In vitro* determinations of clotting times at lower temperatures cause their significant prolongation compared to the determinations of the same samples performed at 37°C. The balance between the clot formation and clot lysis, maintained thanks to efficient processes of fibrin degradation by plasmin, seems unaltered under moderate hypothermia; in febrile conditions, on the other hand, fibrinolysis predominates. Patients with extensive injuries constitute a specific group, in which hypercoagulation develops due to the release of substantial amounts of tissue thromboplastin [49].

However, it should be emphasised that studies aimed at explaining the effects of both deliberate and inadvertent hypothermia on the clotting system present inconsistent results, depending on the methodology applied. Physical isolation of the individual parts of clotting cascade *in vitro* cannot reflect explicitly their *in vivo* function when the relations between them merge at various levels. Likewise, the relation between the extent of hypothermia and intraoperative blood loss is extremely difficult to assess objectively, which results in conflicting findings. In 1996, Schmied et al. and colleagues [50] published their findings indicating possible greater blood loss during hip arthroplasty in cases of perioperative hypothermia. Since that time, both confirming and contradicting data have been published [51], predominantly the former. Despite the fact that the factors such as the course of surgery and experience of a surgeon have significant impact on the above discrepancies, intraoperative temperature should undoubtedly be maintained at the level comparable to the physiological one.

SUMMARY

Despite the lack of its accurate definition, intraoperative hypothermia is likely to be the most common anaesthesia-related complication. Therefore, it is essential for the medical personnel responsible for perioperative safety of patients to be familiar with postoperative consequences of intraoperative thermal disturbances. In many cases, the maintenance of intraoperative normothermia requires much more than just the awareness of this problem. Thanks to the currently available systems preventing intraoperative heat loss (forced air warming, electric heating pads and warmed blankets, circulating set-temperature water devices and devices for warming infusion fluids), there are grounds for hope that patients will leave operating theatres without nagging shivering and with the lowest possible risk of perioperative complications.

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