effect of prostaglandin E2 on shivering thermogenesis under cold stress. We suggest that the increased transcriptional activity of the *PTGS2* gene in the rs689466 T allele may play a role in human adaptation to cold climates.

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SCIENTIFIC REVIEWS AND LECTURES

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UNINTENTIONAL INTRAOPERATIVE HYPOTHERMIA IN ONCOLOGICAL SURGERY AND MAINTAINING NORMOTHERAPY AS PREVENTION OF CARDIAC COMPLICATIONS: THE CURRENT STATE OF THE ISSUE

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A review is done of the latest research on unintentional intraoperative hypothermia (UIH) in oncological surgery, as well as its contribution to cardiac complications. Data are presented on the risk factors for developing UIH, the impact of surgery duration and type, as well as different anesthesia types and methods on the stage of the patient's hypothermia. Data on the relationship between the severity of UIH and the surgical profile of a patient and the patient's comorbidity were studied. It was revealed that cancer patients are at risk of developing UIH in the perioperative period, indicating the importance of preventing hypothermia during the surgery and anesthesia. The results of research on the undesirable effects of UIH, the impact of hypothermia on the development of various events, including cardiac complications, were analyzed. Data on the prevention of UIH and the methods of its prevention were systematized. The potential of maintaining the patient's normothermia for reducing the risk of developing cardiac complications in the immediate postoperative period is shown.

Keywords: unintentional intraoperative hypothermia, cardiac complications, temperature monitoring, active warming, early postoperative period.

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Unintentional intraoperative hypothermia (UIH) is a decrease in core temperature (CT) of the patient's body below 36°C during surgery. UIH is caused by adverse factors of surgical treatment that increase body heat loss (the operating room temperature, immobility of the patient, opening of body cavities and their irrigation with solutions); the initial state of the patient; the severity of the underlying and concomitant pathology; as well as the effect of anesthesia on thermoregulation mechanisms [5].

This article reviews the scientific literature on UIH in oncological surgery, the factors for its development, the complications of UIH, and the methods for its prevention. The search for articles was carried out in public databases published in English and Russian before December 31, 2022. The following terms or their combinations were used as search queries: in Russian – «гипотермия», «анестезия», «непреднамеренная интраоперационная гипотермия», «периоперационная гипотермия», «озноб», «согревание», «активное согревание», «абдоминальная хирургия», «онкология», «онкологическая хирургия», «кардиальные осложнения», «абдоминальная онкологическая патология», «послеоперационное осложнение», «ишемическая болезнь сердца», «нарушения ритма сердца», «ишемическая болезнь сердца»; in English – “hypothermia”, “anesthesia”, “intraoperative perioperative hypothermia”, “unintentional intraoperative hypothermia”, “shivering”, “warming”, “active warming”, “abdominal surgery”, “oncology”, “oncological surgery”, “abdominal oncological pathology”, “postoperative complication”, “cardiac events”, “ischemic heart disease” , "cardiac arrest", "cardiac arrhythmia", and "cardiac complications". To ensure the quality of the search, the selection of relevant studies was done manually, with a selection of articles published predominantly in the past five years.

Incidence, factors and mechanisms for the development of unintentional hypothermia during surgery and anesthesia. According to Sabbag et al., the proportion of patients with temperatures <35°C was 19.1%, those with temperatures <36°C – 64% [27]. In 2017, in a multicenter retrospective study, the all-Russian public organization "The Federation of Anesthesiologists and Resuscitators" analyzed 5,733 case histories of patients in intensive care units (ICU) at various clinical centers of the Russian Federation (Moscow, Novodvinsk, Arkhangelsk, Krasnodar, Yakutsk, and Chita). The study showed that more than 70% of the patients were moved to the recovery room in a state of hypothermia, with the average body temperature of the patients upon admission to the ICU at 33.6°C (between 32.9 and 34.3°C) [13].

Unlike therapeutic hypothermia, which is used in a number of neurosurgical or cardiovascular procedures, UIH occurs spontaneously and is due to multiple factors. First of all, it is a microclimate of the operating room. A decreased temperature of the operating room in winter can be caused by structural defects in walls and windows, as well as insufficient heating; whereas in summer it is due to climate equipment used for creating comfortable working conditions for the surgical team [28]. Therefore, with no passive heating by additional surgical clothing starting from the preoperative room and active heating of the patient during the surgery, their body temperature decreases inevitably.

Undoubtedly, one of the main factors in the development of UIH is the duration and type of surgery. During long abdominal surgeries, UIH is much more frequent, as shown in a study by Sabbaq et al. [27]. During laparotomic surgical interventions, the area of heat dissipation due to the peritoneum increases, and moisture evaporates, which explains the incidence of UIH during open surgery. Surgical peritoneal lavage with saline or room-temperature chlorhexidine bigluconate solution also leads to a rapid decrease in core temperature [8]. However, with longer duration, UIH can also be observed during minimally invasive operations. UIH occurs in 29% of the patients undergoing abdominal closed surgery, according to a study by Chen et al. [32]. In a study by Li, Liang and Feng, hypothermia was detected in 72.7% of adult patients during video-assisted thoracoscopic surgeries [28]. During endoscopic operations, dry and cold carbon dioxide is injected into the abdominal cavity. Carboxyperitoneum may be a risk factor for UIH, since insufflation of dry and cold carbon dioxide reduces the patient's core temperature, as shown by a prospective observational study by Groene et al. [22]. Again, the time factor is of decisive importance. Operations lasting more than 2 hours are characterized by a higher incidence of UIH, which can be considered as a specific risk factor for the development of UIH.

The initial state of the patient, the severity of the underlying pathology for which the surgery is performed, as well as the severity of concomitant pathology and factors such as old age, excessive weight, and others are also of significant importance for the development of UIH [27].

Concomitant chronic pathologies, like diabetes mellitus, hypothyroidism, cardiovascular diseases, worsen the body's thermoregulatory capabilities. Asthenic patients with severe malnutrition are initially most prone to hypothermia, due to metabolic disorders in the body. In this category of patients, preoperative hypothermia guarantees a continued decrease in temperature during surgery and can lead to serious consequences.

In elderly patients, hypothermia is more pronounced, since anesthetics demonstrate more pronounced vasodilatory effect on people over 60 years of age [18]. Today, such preoperative characteristics as age, height, weight, high scores by the ASA (American Society of Anesthesiologist) scale, heart rate and systolic blood pressure are considered to be prognostic signs of UIH [17].

Of direct importance in the initiation of hypothermia is anesthetic support, which contributes to violated thermoregulation. In a healthy awake person, the body temperature is maintained by behavioral and vegetative regulation when the threshold temperature is reached. During anesthesia, there are no behavioral reactions and only the vegetative mechanism of body defense and external control of thermoregulation are implemented [5]. Normally, the threshold temperatures for vasoconstriction and shivering are 36.5-36°C, respectively, which decrease by 2-3°C during general anesthesia. In addition, autonomic reactions worsen, since most anesthetics increase thermal response and reduce cold threshold reactions; the “inter-threshold range” can increase 10-fold (from 0.3°C to 2-4°C), which delays the start of the thermoregulatory defense mechanism.

The main mechanism of hypothermia during general anesthesia is vasodilation (with simultaneous suppression of vasoconstriction), which occurs in response to numerous drugs that are part of the premedication (opioid analgesics, benzodiazepines), induction (propofol, sodium thiopental), or inhalation anesthetics to maintain anesthesia (sevoflurane, isoflurane, desflurane) [5]. Vasodilation shifts the centralized blood flow to the periphery, which disrupts the leading mechanism for maintaining temperature homeostasis. In the periphery, warmed central blood consumes the accumulated heat through irradiation, which leads to a gradual decrease in core temperature of the body [5]. In addition, the infusion of insufficiently heated solutions reduces the temperature of circulating blood [28].

There are three phases in the development of hypothermia during anesthesia: the initial rapid decrease, the slow linear decrease, and the plateau phase [5]. The first phase is observed in the 1st hour of anesthesia and is characterized by a decrease in CT by 0.5-1.5°C and a simultaneous increase in peripheral temperature from 33 to 35°C due to vasodilation and redistribution of heat from the center to the periphery. The second phase of hypothermia, in the next 2-4 hours of the surgery, is due to the excess of heat loss over metabolic heat production. After 3-4 hours, the plateau phase follows, when body temperature stabilizes, since peripheral vasoconstriction initiated by a decreased body temperature reduces both metabolic heat production and heat transfer from the core to the periphery [26].

Violation of thermoregulation is also observed during neuraxial anesthesia, when the patient's behavioral response and the autonomic defense mechanism are also excluded. Like with general anesthesia, spinal anesthesia is characterized by decreased threshold values of thermoregulation and thermal redistribution from the core to peripheral tissues. With the use of this method of anesthesia, another mechanism of hypothermia is the blockade of the sensory impulse about a reduced temperature from blockade zones to thermoregulatory centers. A significant predictor of core hypothermia during spinal anesthesia is the level of blockade. The correlation between high blockade and low core temperature during spinal anesthesia is consistent with the known physiological effects of spinal anesthesia: the larger the area of blockade, the greater the expected impaired thermoregulation [26].

Given these data, it can be assumed that the combination of general anesthesia with regional anesthesia will increase the risk of intraoperative decrease in body temperature.

An analysis of the literature on UIH shows that the problem of hypothermia is also relevant for cancer patients. Thus, a study by the Morozumi's group revealed that intraoperative hypothermia occurs quite often and, moreover, can be an important predictor of recurrence and survival in stage II muscle invasive bladder cancer [23]. In this study, 68 (55%) of 124 patients who experienced hypothermia during radical cystectomy, with no difference in the number of postoperative complications, had a higher recurrence rate within 12 months (p=0.013).

Analyzing the results of two-year survival after radical cystectomy in 852 patients, the study by Timothy et al. led to opposite conclusions [16]. In this study, despite active rewarming with the Bair Hugger patient warming system, UIH was registered during surgery in 274 (32%) patients, among whom 37 (4.3%) patients had profound hypothermia (t<35.0°C). At the same time, there was no statistically significant association of hypothermia with two-year survival, excluding UIH as a predictor of cancer outcomes among the patients undergoing radical cystectomy.

An analysis of 1,547 colorectal procedures revealed that the incidence of intraoperative hypothermia was 67.0% and was higher for laparoscopy than for laparotomy (71.23% vs. 63.16%; chi-square *P* = 0.001). In addition, there were significant differences in the severity of hypothermia [25].

The relationship between body weight and the incidence of UIH is evidenced by a study by Motamed et al., who showed that the average incidence of hypothermia was 21% in the patients operated on for breast neoplasms. At the same time, the body mass index (BMI) was significantly lower in the hypothermia group – 23.5 ± 4.1 compared to 26.4 ± 6.1 kg/m^2 in normothermic patients (p<0.05) [21].

In 2018, a group of researchers led by Tai conducted a similar study on mice, the results of which indicated that there is a significant risk of metastases in case of sepsis induced by hypothermia and massive blood loss [33].

Thus, cancer patients may represent a specific group in terms of the risk for developing perioperative hypothermia.

Complications of unintentional intraoperative hypothermia. Hypothermia during surgery is not a physiological condition and can be accompanied by adverse effects both during surgery and lead to undesirable consequences in the postoperative period. It is now recognized that perioperative hypothermia can have a negative impact on many vital systems of the human body [5]. Hypothermia has been proven to be involved as a factor that reduces the activity of the blood coagulation system, increases the likelihood of cardiac arrhythmias, myocardial ischemia, increased blood loss, increased duration of postoperative wound healing, the occurrence of septic complications, which together increases the total number of complications, the consumption of medications, the duration of hospitalization, and postoperative mortality [16].

With UIH, there are also violations of the blood coagulation system. The studies by Tsarev revealed a dependence of the risk for developing coagulopathy (decrease in the values of the international normalized ratio) on hypothermia in patients with polytrauma [2]. A decreased activity of the coagulation system factors results in bleeding of wounds, which in the future leads to repeated interventions and the need for blood transfusions.

A meta-analysis of 384 studies conducted by a group of scientists from the PRC showed that perioperative hypothermia can significantly increase the risk for surgical infection [15]. Poveda et al. did a detailed review with a meta-analysis of 956 publications of 9 studies that were devoted to the study of the relationship between intraoperative warming of patients and infectious complications and are available in the PubMed, CINAHL, LiLACS, CENTRAL and EMBASE databases. They came to the conclusion that additional randomized clinical trials are needed. trials to evaluate the effectiveness of UIH prevention as a factor in preventing infection in the surgical site [24].

Hypothermia leads to prolonged effects of anesthetics and muscle relaxants, later awakening time and delayed extubation of patients.

Hypothermia changes the level of potassium in the blood serum. An analysis of 50 clinical and experimental studies evaluating the effect of hypothermia on potassium levels, performed by Buse et al. identified the main pathophysiological mechanisms that explain fluctuations in blood potassium levels with temperature [30]. At the beginning of hypothermia, hypokalemia is observed, associated with its intracellular shift due to increased functioning of the Na, K-ATPase, beta-adrenergic stimulation, pH shift, and membrane stabilization. Then, with aggravation of hypothermia due to insufficient activity of enzymes, an increased level of potassium occurs.

The most formidable complications of hypothermia occur in pronounced, severe forms of hypothermia, when core temperature drops below 35.2°C. A decreased body temperature leads to spasm of the coronary vessels, an increased oxygen consumption by the heart muscle, which can lead to myocardial ischemia. Cardiac arrhythmias are potentially life-threatening for the patient and may result in cardiac arrest [10]. Hypothermia during surgery leads to a slower impulse conduction, which can lead to varying degrees of atrioventricular block. Postoperative shivering and tachycardia also negatively affect the cardiovascular system, increasing myocardial oxygen demand and exacerbating existing cardiac pathology, especially in debilitated patients [12].

Currently, cardiology guidelines consider adequate correction of perioperative hypothermia and prevention of postoperative shivering to be important components of anesthesia management as a method of preventing myocardial injury [4].

There is no doubt that the number of negative consequences of UIH will depend not only on the surgical access, but also on the number and depth of comorbidities. Thus, high-risk patients should include oncological patients, who are characterized by weight loss, residual intoxication due to chemotherapy prior to surgery, and often concomitant chronic pathologies, cardiovascular diseases in particular [10], with 78.2% of oncological patients having concomitant coronary artery disease [12]. Hypothermia is also often accompanied by cardiac arrhythmias and arterial hypertension, and triples the incidence of myocardial ischemia [11].

It should be noted that in most cancer patients, surgical treatment is preceded by radiation or chemotherapy. At the same time, the basic chemotherapy drugs used in the treatment of neoplasms have a wide range of toxic effects, including cardiotoxicity, causing damage to cardiomyocytes, endocardium and heart valves, development of myocardial dysfunction and/or heart failure. The incidence of complications, the onset of clinical manifestations, and the severity of manifestations of toxicity vary depending on the selected anticancer treatment, the dose of the drug, and the presence of concomitant cardiovascular diseases. The combination of chemotherapy or their combination with radiation therapy can aggravate the cardiotoxic effect [7].

As proven by the study on the impact of UIH on the cardiac complications incidence, unintentional hypothermia is an independent risk factor for early postoperative complications. Thus, a retrospective analysis of 121 cases of radical esophagectomy revealed that 51 (96.2%) out of 53 patients with early postoperative complications had UIH. Among the complications, 8 cases of cardiac arrhythmia were recorded, making 11.1% of all early postoperative complications.

The study of UIH as a predictor of early postoperative complications in patients with bladder cancer who underwent cystectomy showed its significance in the development of various complications [11]. The study involved 124 patients, of which 68 (54.8%) patients experienced hypothermia during surgery. Complications were observed in 22.1% of the patients who experienced hypothermia and in 14.3% of the patients without hypothermia. At the same time, cardiac complications were noted in 12.5% and 6% of cases, respectively, in groups with and without hypothermia.

Therefore, the presented data show a close relationship between UIH and postoperative complications, including cardiac complications, in cancer patients, which indicates the importance of preventing hypothermia at the stages of surgery and anesthesia.

Prevention of unintentional intraoperative hypothermia and methods of warming patients. Undoubtedly, the methods of active rewarming of patients in the perioperative period significantly affect the severity of UIH and its complications [4]. However, at present, despite the relevance of the problem with UIH, intraoperative thermometry has not yet become a routine practice in anesthesiology, like a control of hemodynamics or respiration. Studies around the world indicate low compliance with recommendations for temperature management in the perioperative period. For instance, according to the European group TEMMP (Thermoregulation in Europa Monitoring and Managing Patient Temperature), which studies the compliance with the temperature regime of patients undergoing surgical interventions, special warming methods in the perioperative period are applied to only 20% of patients [18].

Currently, UIH prevention uses methods aimed at various mechanisms of hypothermia in each phase of the perioperative period [34, 29]. In order to prevent the occurrence of UIH, a number of clinics have developed guidelines for the personnel of operating and anesthesia teams [20]. The FAST TRACK strategy for accelerated surgical treatment and rehabilitation, which is widely implemented in world and Russian medicine, includes mandatory temperature management and prevention of perioperative hypothermia [6]. The latest orders of the Ministry of Health of the Russian Federation on the procedure for providing medical care in the field of "anesthesiology and resuscitation" regulate the presence of insulating blankets in the operating room and in the recovery room of the intensive care unit [8, 9].

Today, it is recommended to start warming from the moment the patient enters the preoperative room [14]. For example, following the recommendations of the Association of Scientific Medical Societies in Germany on pre-warming of patients has led to a considerable and clinically significant reduction in the incidence of UIH. Currently, the incidence of hypothermia in German clinics is 15.8% during surgery and 5.1% after surgery [17].

To preserve the accumulated heat, the patient is covered with heat-insulating blankets before the surgery; special blankets with active warming mechanisms and blankets with chemical reagents have been developed, the operation of which does not require an additional power source or heating control unit [36]. Active heating systems are also applied, using warm air blown under clothing or a drape, which further reduces the severity of hypothermia during surgery [31].

After providing vascular access, at the stage of anesthesia induction, it is proposed to use heated solutions for intravenous infusions, since a certain amount of heat is spent on warming the infusion media entering the body. Therefore, rewarming with infusion solution can be used as an additional measure to rewarm the patient [3]. According to the data obtained by Stolyarov and his colleagues, correction of perioperative hypothermia by heating solutions in emergency surgical patients in 92.4% of cases prevents perioperative hypothermia and its clinical manifestations [4]. Beccera et al. believe that even short-term, for 5-15 minutes, preliminary active warming of the patient before laparoscopic urological surgery allows maintaining a significantly higher temperature during the intraoperative period compared to patients who are not pre-warmed [33]. Yoo et al. consider active forced heating with air at a temperature of 47°C at the heater output from the induction period as a simple and effective method for preventing UIH during surgeries lasting more than 120 minutes [19].

In open surgical interventions, the use of heated solutions for cavity irrigation is proposed, which reduces the combined losses caused by moisture evaporation and heat convection from the cavity. In closed surgical interventions, it is also necessary to use heated and humidified carbon dioxide during insufflation into the abdominal or pleural cavities. The heated gas prevents the development of intraoperative hypothermia, maintains the patient's basal body temperature, and may even increase it [35].

A noteworthy fact is the development of hypothermia during surgery even in patients who are subjected to active warming methods. In fact, hypothermia occurs not only during the surgery itself, but begins to develop even at the preparatory stage for the surgery: during the preparation of the patient, introduction to anesthesia, and can also continue in the first hours after the surgery in the recovery room or in the intensive care unit. Therefore, many researchers studying UIH emphasize the need to develop methods for predicting and identifying the patients at risk of intraoperative hypothermia; optimizing measures for thermoregulation; and the need for additional research on studying methods of active warming and introducing innovations in the technology of active warming of patients [1].

Conclusion. Hypothermia in the perioperative period remains one of the relevant issues in modern anesthesiology [3]. An analysis of the studies presented in the literature on the incidence of UIH and its role as a factor contributing to the development of complications affecting the treatment outcomes for surgical patients shows that UIH is often studied in a generalized group of patients, without distinguishing individual nosological categories. To date, in oncological patients, the temperature profile when using various methods of intraoperative active warming and the effect of UIH on the development of cardiac complications have not been sufficiently studied, and data on core temperature depending on the methods of surgical access in the perioperative period have not been presented. There is inconsistency in the data, which can be explained by the heterogeneity of the sample of study groups in terms of underlying and concomitant diseases, types of surgeries, age, and other factors.

Considering the foregoing, monitoring of core temperature and assessing the effect of UIH on the development of cardiovascular complications in patients with oncological pathology is relevant, and prevention of cardiac complications based on maintaining normal core temperature in the perioperative period seems a promising and needed research.

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