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REVIEW
ОБЗОРНАЯ СТАТЬЯ

Physiological features of cells and microvasculature under the local hypothermia influence

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Abstract. Hypothermia or cold therapy is the local or systemic application of cold for therapeutic purposes. Local application of cold is used to control inflammation: pain and swelling, hematoma and trismus reduction. Despite the frequent use of cooling in prosthodontic rehabilitation and in physical therapy, as evidenced by many reports in the literature, there is scientific documentation that suggests disadvantages of using this treatment in maxillofacial surgery and oral surgery. Also the clinical studies that have been carried out in maxillofacial surgery and oral surgery have been conducted in an empirical manner, which casts doubt on the results. In view of this, it is relevant to study the mechanisms of microcirculatory preconditioning and hypothermia. This physiological process is so interesting for the development of medical devices of controlled hardware hypothermia to prevent inflammatory symptoms at the stage of rehabilitation by targeting the vascular and cellular component of the inflammatory process in different areas of the human body. To date, the use of local hardware controlled hypothermia in various pathological conditions in humans is a topical trend in medicine. Microcirculatory bloodstream is directly related to temperature factors. Although there are concepts of vascular spasm or dilatation in the microcirculatory bloodstream during systemic hypothermia, there are no reliable data on the cellular and vascular reactions during local hypothermia. In this paper, a search for fundamental and current scientific work on the topic of cellular and vascular changes under the influence of hypothermia was conducted. The search for data revealed that the mechanisms of intracellular hypothermia are of particular interest for the development of therapeutic treatments after surgical interventions in areas with extensive blood supply. With this in mind, it is relevant to investigate several areas: the role of endothelium, glycocalyx and blood cells in microcirculatory-mediated preconditioning and intracellular hypothermia, and in the molecular mechanism that regulates these processes, whether they occur in the same way in all tissues.

Keywords: therapeutic hypothermia, microcirculatory bed, vasodilation, vasospasm, cellular hypothermia

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Therapeutic hypothermia. Historical sketch

The idea that cooling a person can slow down biological processes and therefore death was first described by Hippocrates (around 450 BC), who advised laying wounded soldiers in the snow. In the early 1800s, during the French invasion of Russia, a military surgeon observed that wounded soldiers placed closer to fires died earlier than those who placed in colder bunks. During this period cryoanalgesia was also used for amputations and surgeons noticed that hypothermia not only acts as an analgesic but also slows bleeding. Clinical interest in the use of therapeutic hypothermia began in the 1930s with reports of cases of drowning that were successfully resuscitated despite prolonged asphyxia [1].

In 1943 Temple Fay published one of the first scientific papers on therapeutic hypothermia. The author observed improvement in patients after craniocerebral trauma (CCT) when the temperature was lowered from 38.3 to 32.7 degrees Celsius. In the 1950s and 1960s clinical trials using very deep hypothermia were initiated but were soon discontinued due to side effects. In the 1990s, moderate hypothermia was used in three cases of cardiac arrest after successful resuscitation, and in all three cases there was complete recovery without residual neurological damage [2]. Therapeutic hypothermia began to attract attention after two prospective randomised controlled trials, published in the New England Journal of Medicine in 2002, showed significant improvements in short and long-term survival as well as neurological outcomes [3]. Today, the term «targeted temperature management» (TTM) is used instead of therapeutic cooling. TTC can be used to prevent fever, maintain normothermia, or induce cooling.

Three decades of research on animals have shown that hypothermia has a strong cerebroprotective effect. The success of hypothermia in acute brain injury research has not only stimulated continued interest in investigating mechanisms, but has also generated a surge of new interest in elucidating the beneficial signalling molecules that play an important role in cooling [4].

Systemic hypothermia is a treatment option after cardiac arrest, and the neuroprotective benefits of systemic hypothermia after cerebral ischaemia have been demonstrated [5, 6]. Duan, Honglian have proposed the use of local endovascular infusion of cold saline directly into the infarct focus using a microcatheter. In small animal models, the procedure has shown incredible neuroprotective promise [7]. Although total hypothermia is recognized as a clinically applicable neuroprotective treatment, moderate local hypothermia after spinal cord injury is considered a more effective approach. Teh, Daniel Boon Loong et al. (2018) investigated the feasibility and safety of inducing prolonged local hypothermia in the central nervous system in a rodent model. The results showed significant recovery of somatosensory potential amplitudes in groups with local hypothermia [8].

Vipin, Ashwati et al. (2015) demonstrated the neuroprotective effect of short-term moderate total hypothermia by improving electrophysiological and motor parameters as well as histological examination after spinal cord injury in rats. The advantage of short-term local hypothermia over short-term general hypothermia after acute spinal cord injury has also been shown [9]. Lewis, S. R. conducted a meta-analytic review of the scientific evidence and found that mild hypothermia in CMT correlates with such indicators as mortality, and complications after brain surgery. Despite the large number of studies, there is still no qualitative evidence that hypothermia is beneficial in the treatment of people with CHT. Further research is needed in this area, which is methodologically robust,

to establish the effect of hypothermia in people with CHT [6].

Today the therapeutic hypothermia methods can be divided into physical and pharmacological methods. Physical methods are based on devices designed to cool the whole body or its parts. Various means of surface application are used: cooling jackets, water-cooled mattress covers, cooling pillows, ice packs, etc. [10], which work slowly and require a large amount of time, a certain temperature range. Internal cooling agents in the form of intravenous fluids are also used, which provide a rapid decrease in body temperature [11], but these methods cannot be used outside the hospital. In addition, the above-mentioned body cooling methods can cause electrolyte imbalances, cardiovascular dysfunction [12] and promote infections such as pneumonia [13, 12].

Thermoregulation and hypothermia

Thermoregulation is a vital function of the autonomic nervous system in response to cold and heat stress. The physiology of thermoregulation maintains homeostasis in the human body by maintaining an internal body temperature of 37 °C, which ensures normal cell function. Heat production and dissipation depend on a coordinated set of autonomic responses. The clinical detection of impaired thermoregulation provides important diagnostic and localized information in the assessment of disorders that disrupt thermoregulatory pathways, including autonomic neuropathies and gangliopathies. Failure of neural thermoregulatory mechanisms or exposure to extreme, or prolonged, temperatures that inhibit the body's thermoregulatory abilities can also lead to potentially life-threatening deviations from normothermia. Overcooling, defined as an internal temperature <35.0 °C, can be manifested by shivering, respiratory depression, cardiac arrhythmia, impaired mental function, mydriasis, hypotonia and muscular dysfunction, which may progress to cardiac arrest or coma.

Cold stress causes an indirect increase in vascular tone in the peripheral region of the human body, which reduces heat loss to the external environment to maintain thermal homeostasis. Prolonged exposure to cold can lead to impaired function, but moderate controlled hypothermia has found its application [7, 14]. The era of targeted controlled hypothermia, with an emphasis on a wider temperature range (33—36 °C) shows benefit in acute craniocerebral trauma.

The physiological processes of local tissues under the influence of local hypothermia are poorly understood. Local adaptive changes in tissues occur under the influence of temperature exposure by virtue of many factors. Some of these factors are vascular, hormonal, stress-protein adaptive systems [15].

The origin of cold-induced vasodilation is still a big question. This process may take place via a central pathway, or locally through direct cold paralysis of the peripheral vessels (CPPV). However, we should not forget arteriovenous anastomoses, which also play a major role [16].

There is also evidence that the CPPV has a cryoprotective function against local cold damage. For example, hypothermia is known to reduce the metabolic rate by 5–7 % when the internal body temperature decreases by 1° [17], which reduces cellular oxygen consumption. This is one of the main mechanisms underlying the protective action of therapeutic hypothermia, since oxygen starvation and the accumulation of lactate and other wastes of anaerobic metabolism play a central role in the progression of ischemic cell death. The accumulation of aspartate, glutamate and other excitatory neurotransmitters plays an important role in neuronal death after cerebral ischemia [18]. In animal models it was shown that glutamate release after cerebral ischemia depends on temperature conditions. Mild to moderate hypothermia is associated with the most significant decrease in glutamate levels compared to severe hypothermia and hyperthermia [19]. Hypothermia reduces free radical production and suppresses various inflammatory processes following global ischemia and reperfusion. Reperfusion causes a significant increase in the production of free radicals such as hydrogen peroxide, superoxide, nitric oxide and hydroxyl radicals. High levels of oxidants, cause disruption of redox balance throughout the body and induce peroxidation of lipids, proteins and nucleic acids, which contributes to cellular damage [20]. One study using an *in vitro* model of cerebral ischemia showed that the neuroprotective effects of hypothermia

were associated with a significant reduction in nitric oxide and superoxide formation when the temperature decreased to 31–33 °C [21]. The inflammatory response that follows reperfusion has both positive and negative effects. However, decompensation can last for 5 days, and persistently high cytokine level is devastating over this long time lap. Hypothermia suppresses the inflammatory cascade and, in turn, prevents exacerbation of cellular damage by inflammation.

The regulation of cutaneous blood flow occurs due to the complex and dynamic interaction of body (core) and sheath thermal interactions. In other words, there are concepts of external and internal heat. However, the intensity of vasomotor reactivity to localized thermal stressors is primarily determined by the thermal state of the whole body [22]. In particular, during prolonged exposure to cold, hypothermia-induced sympathetic excitation dominates over vasomotor control in the extremities; noradrenergic constriction of cutaneous arterioles prevails, while the frequency and magnitude of CPPV response are impaired [23].

Under conditions of thermoneutral rest, systemic hypoxia increases the activity of sympathetic innervation and causes vasoconstriction on the outer layers of the skin. Consequently, and based on epidemiological studies, hypoxia was and is considered to be a predisposing factor for the development of local cold injury [24]. However, laboratory studies have shown that hypoxic vasoconstriction in the outer layers of the skin is less pronounced than vasoconstriction caused by a localized cold stimulus [25]. Lingering constrictor effect is mediated by hypoxia, a delay in spontaneous warming of the limb after local cooling [26].

At high altitudes, hypoxia is usually exerted with low ambient temperature, which blunts peripheral vasoconstriction by increasing the rate and magnitude of core cooling. However, the simultaneous effect of hypoxia and low temperature on vasomotor reactivity remains an open question.

Hypothermia and vascular response

Normal vascular microcirculation is a network of perfused capillaries characterized by minimal heterogeneity, although its extent depends on the metabolic demands of the surrounding tissues. Adaptation to metabolic demands occurs through capillary opening and closing, and modulation of precapillary sphincters is partially influenced by systemic factors [27]. Thus, the microcirculation links the macrocirculation to the cells, facilitating and mediating perfusion of target organs.

Cutaneous blood flow in humans and warm-blooded animals is reduced when exposed to cold. This reaction is usually explained by the fact that reflex-exogenous temperature increase leads to sympathetic tone if cooling threatens to decrease body temperature. Local cooling increases the tone of superficial cutaneous limb veins in proportion to the cooling temperature and is independent of alpha-adrenergic innervation. Cutaneous arterial vasodilation showed the opposite pattern, which was expressed by vasodilation, also not mediated by innervation. Locally cold induced vasoconstriction is the result of a myogenic response and is due to transcellular ion translocation [28].

The effects of temperature on vascular responses to certain agonists such as noradrenaline [29, 30], 5-HT [31, 32], potassium channels [33] and acetylcholine [34] have previously been studied in details. On the other hand, the direct local effect of temperature on vascular tone has scarcely been studied. Vascular contraction induced by cooling has been studied in samples such as rat bladder smooth muscle [35], sheep tracheal muscle [36] and intracerebral arterioles [37]. These studies have established that cooling can affect calcium homeostasis by preventing translocation of extracellular and intracellular calcium. However, there is no extensive information about the mechanisms involved in hypothermic perfusion.

Herrera, B et al. (2000) have shown that hypothermia causes contraction of an isolated renal artery. The response of smooth muscle to cooling in different body organs has been studied [38]. The results showed that cooling has a pronounced effect on smooth muscle. Therefore, it has been hypothesized that elastic fibers are responsible for the atypical relaxation induced by cooling.

Hypothermia causes relaxation of deep vessels such as aorta, pulmonary artery, carotid artery and spasm of superficial vessels [39]. Herrera, B. (2002) showed the role of elastic fibers in various responses of certain vessels when cooling from 37 to 8 °C. Previous results have shown that the nature of the vessel (conduit or muscle vessel) determines the different behavior (dilatation or spasms) of isolated vessel segments when the temperature decreases from 37 to 8 °C [40]. Vessels with a large number of elastic fibers show dilatation upon cooling. On the other hand, muscle vessels with fewer elastic fibers undergo contraction. Calcium release from intracellular depots causes arteries to contract during cooling. Vasodilation occurs only when smooth muscle contraction mechanisms are inactive, as in the case of vessels that have been subjected to cold storage for 48 hours. The results presented in the author's work confirm the presence of two main effects, which are directly dependent on the type of vessel. In arteries, temperature reduction induces vascular relaxation depending on the elastic component of the vascular wall. In muscular vessels, the predominant effect is contraction due to an increase in intracellular calcium. Cooling-induced spasm occurs due to the maintenance of balance of muscle cell metabolism and vascular wall tone.

Stepwise cooling of rabbit carotid arteries caused dilation proportional to temperature [41].

In order to investigate the underlying mechanism of temperature responses in the carotid artery at the cellular level, blocking experiments were carried out that revealed the critical involvement of potassium channels (K^+ channels), important regulators of smooth muscle function and hence of vascular lumen width. Their activation induces a major vasodilatory mechanism through membrane hyperpolarization, whereas their inhibition induces vasoconstriction. Four different types of K+-channels have been identified in arterial smooth muscle [42].

Hemodynamic monitoring of critically ill neonates mainly focuses on systemic arterial oxygen saturation. Cellular hypoxia and poor tissue perfusion may be present in these neonates. Ideally, hemodynamic monitoring should provide information on whether cells are receiving enough oxygen to maintain cellular mitochondrial respiration.

Near-infrared spectroscopy (NIRS) is a promising technique by which real-time monitoring of the cerebral perfusion in neonates can be performed [43]. The depth of the NIRS measurement is 1–3 cm, depending on the design of the probe. Fredly, Siv (2016) investigated differences in skin microcirculation and its ability to deliver oxygen during cooling and after warming in neonates with or without high levels of C-reactive protein (CRP). Twenty-eight infants were divided into two subgroups based on low or high CRP (recurrent values above 30 mg/l for more than 24 h). Differences between the two groups with regard to laser Doppler perfusion measurements (LDF), computer video microscopy and diffuse reflectance spectroscopy during hypothermia on days 1 and 3 and after hyperthermia on day 4 were assessed. After hyperthermia, children with high SRB levels had significantly higher cutaneous perfusion LDF, lower functional vessel density and greater heterogeneity in capillary blood flow velocities compared to children with low CRP levels, while no such differences were found during cooling, suggesting a positive anti-inflammatory effect of hypothermia on cutaneous blood flow [44]. Caminos Eguillor et al. (2021) studied the effect of hypothermia on microcirculation in normal and severe hemorrhagic shock. The authors concluded that hypothermia did not additionally inhibit the microcirculatory disturbances caused by hemorrhagic shock, which contradicts the benefits of therapeutic hypothermia [45]. However, in healthy humans, microcirculation maintains cellular homeostasis through preconditioning. When blood volume decreases, subsequent microcirculatory changes result in heterogeneity of perfusion and tissue oxygenation. Initially, this is partially compensated by preserved autoregulation and increased cellular metabolic rate, but in later stages the loss of autoregulation activates the intracellular hypothermia cascade [46].

A review of the literature revealed that, due to the unclear topic of the vascular response to cold, the several biomedical mechanisms involved in hypothermia are relevant. The type of vessel involved in procedures,

such as post-operative local hypothermia, should also be considered [47].

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Физиологические особенности клеток и микрососудистого русла под влиянием локальной гипотермии

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Аннотация. Гипотермия или терапия холодом является местным или системным применением холода в терапевтических целях. Местное применение холода используется для контроля воспалительного процесса: боли и отека, гематомы, снизить тризм. Несмотря на частое использование охлаждения в ортопедической реабилитации и физиотерапии, о чем свидетельствует множество сообщений в литературе, существуют научные данные, которые говорят о недостатках

применения в челюстно-лицевой хирургии и хирургической стоматологии. Также клинические исследования, которые проводились на базе челюстно-лицевой хирургии и хирургической стоматологии, проводились эмпирическим путем, что ставит под сомнения результаты исследования. Ввиду этого актуально изучение механизмов микроциркуляторного прекондиционирования и гипотермии. Данный физиологический процесс представляет особый интерес для разработки медицинских устройств контроллируемой аппаратной гипотермии для предотвращения воспалительных симптомов на этапе реабилитации, целенаправленно воздействуя на сосудисто-клеточный компонент воспалительного процесса в разных областях тела человека. На сегодняшний день применение локальной аппаратной контролируемой гипотермии при различных патологических состояниях человека актуальное направление в медицине. Микроциркуляторное русло напрямую связано с температурными факторами. Несмотря на то, что существуют понятия сосудистых спазма или дилятации в микроциркуляторном русле при системной гипотермии, отсутствуют достоверные данные по клеточно-сосудистым реакциям при локальной гипотермии. В данной работе проведен поиск фундаментальных и современных научных работ на тему клеточно-сосудистых изменений под влиянием гипотермии. При поиске данных было выявлено, что механизмы внутриклеточной гипотермии представляет особый интерес для разработки терапевтических методов лечения после оперативных вмешательств в областях с обильным кровоснабжением. Исходя из этого актуально проведение исследований, направленных на изучение нескольких направлений: роль эндотелия, гликокаликса и клеток крови в микроциркуляторно-опосредованном прекондиционирования и внутриклеточной гипотермии, а также при молекулярном механизме, регулирующем эти явления, одинаково ли они проходят во всех тканях.

Ключевые слова: терапевтическая гипотермия, микроциркуляторное русло, вазодилятация, вазоспазм, клеточная гипотермия

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