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Microwave Radiothermometry in Evaluating Brain Temperature Changes (Review)

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Summary

Aim. This review aims to inform physicians of different specialties (anesthesiologists, intensivists, neurologists, neurosurgeons, oncologists) about the diagnostic capabilities of microwave radiothermometry, which enables to identify and analyze features of alterations of cerebral temperature in brain damage.

The review displays a critical analysis of 80 recent Russian and foreign open access publications found by keywords.

The review presents major clinical features and pathophysiological mechanisms of cerebral thermal balance disruptions in brain lesions. Slow responsiveness and vulnerability of cerebral thermal homeostasis regulation mechanisms that underlie development of different temperature heterogeneity levels in the cerebral cortex in healthy brain and brain lesions are highlighted. The authors postulate their concept about the critical role of hyperthermia in the pathogenesis of brain damage and disruption of interconnections in the global central regulation system. A body of evidence explaining direct association between the depth of consciousness impairment and degree of cerebral cortex temperature heterogeneity manifestation is presented. It is emphasized that a significant increase in temperature heterogeneity with areas of focal hyperthermia accompanies an acute period of ischemic stroke, while in post-comatose state usually associated with prolonged impairment of consciousness, the temperature heterogeneity significantly subsides. It has been suggested that lowering of an increased and rising of the reduced temperature heterogeneity, for example by using temperature exposure, can improve altered level of consciousness in patients with brain damage. The diagnostic capabilities of various technologies used for cerebral temperature measurement, including microwave radiothermometry (MWR), are evaluated. Data on high accuracy of MWR in measurement of the cerebral cortex temperature in comparison with invasive methods are presented.

Conclusion. In healthy individuals MWR revealed a distinct daily rhythmic changes of the cerebral cortex temperature, and badly violated circadian rhythms in patients with brain lesions. Since MWR is an easy-to-perform, non-invasive and objective diagnostic tool, it is feasible to use this technology to detect latent cerebral hyperthermia and assess the level of temperature heterogeneity disruption, as well as to study the circadian rhythm of temperature changes.

Key words: grain temperature balance; cerebral lesions; microwave radiothermometry; MWR Conflict of interest. The authors declare no conflict of interest.

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Introduction

Body temperature is an essential integral parameter of general body condition, its functional activity and regulatory status. Temperature homeostasis in warm-blooded animals is characterized by very high thermal heterogeneity, typical for both homoeothermic core and thermal envelope sections [1]. The temperature of surface tissues largely depends on the ambient temperature, while in the compartments of the thermal center, including internal organs, spinal cord and brain, the differences in temperature are determined by local metabolic activity and the intensity of blood flow, which provides elimination of excess heat into the external environment [2]. The circulatory system levels out the internal temperature gradients in the major arteries such as a rta and pulmonary artery to 37±0.1°C in the normal ranges at rest and under thermoneutral conditions, which does not exclude internal thermal heterogeneity most evident in the brain [3].

Cerebral blood flow is mostly autoregulated, and its changes in response to inner requirements are relatively independent of the systemic circulation within certain limits of arterial pressure variations [4]. The relative independence of the cerebral blood flow from the systemic circulation underlies such independence of cerebral and basal temperature regulation, the values of which can differ significantly [5, 6].

Temperature differences between deep and superficial brain structures, as well as excited and relatively quiescent areas, can be as high as several degrees [7].

Temperature recording is a valuable tool for diagnosis and prognosis in various brain diseases

[8]. In neurogenic fever, latent cerebral hyperthermia without increase in the basal temperature often develops, which may result in underestimation of its impact on disease severity and outcome [9, 10]. Thermal balance disorders are associated with the severity of brain damage, and cerebral temperature is an important marker of the latter [11, 12].

Methodological issues may limit the use of cerebral thermometry in clinical practice. The use of invasive thermometry techniques is acceptable only in neurosurgical patients. It is the most accurate method of temperature measurement, but implantable thermoresistors provide temperature data only in the area of measurement, making it impossible to assess the severity of the thermal imbalance throughout the brain [13]. In addition to thermoresistors, technologies based on radio-emission detection sensors [14] and fiber-optic methods [15], which are still under development, can be employed for invasive temperature sensing.

The most advanced and informative method is proton NMR spectroscopy [16], which provides non-invasive data on brain temperature. However, this technology is labor-intensive and not suitable for monitoring [17]. A previously developed method of thermoencephaloscopy based on registration of infrared electromagnetic radiation (EMR) from the scalp allows the identification of warmer and cooler areas of cortical projections, but gives no idea of the true temperature [18]. Radiometric thermometry using sensors placed on the skin of the forehead has been developed, but still requires careful validation [19].

Microwave radiation thermometry (RTM) is a simpler and more informative method of temperature measurement based on the determination of the intrinsic EMR power of deep tissues [20]. The RTM allows EMR measurements in any body region and at different time intervals [21, 22]. The technique is safe and has no adverse impact on the patient. At present, it is used in a limited way for research purposes to diagnose diseases associated with local temperature elevation [23] and to control the depth of therapeutic hypothermia [24].

The aim of the review is to update specialists in various fields (anesthesiology, intensive care, neurology, neurosurgery, oncology) on the diagnostic performance of microwave radiation thermometry, which allows the identification and analysis of cerebral thermoregulatory disorders in brain injury.

Microwave Radiation Thermometry in Medicine

The first microwave radiation thermometers were developed for radio astronomy in the midtwentieth century [25], and the principle of radiation thermometry was soon used in medicine for the early diagnosis of breast cancer [26].

In contrast to conventional infrared thermography, which can only estimate temperature changes in superficial skin layers [27], measuring the EMR power of human tissues in the microwave range ($\lambda = 3{-}60$ cm, frequency 109–1010 Hz) allows the determination of internal temperature values.

In the radio range, the intensity of radiation is directly proportional to temperature. Therefore, with the measured power of EMR registered by special antennas placed directly on the skin surface of a biological object, it is possible to obtain information by non-invasive estimation of the internal temperature.

In the medical literature, the terms «brightness» or «core» temperature, which correspond to the true thermodynamic temperature, are most commonly used [28]. When calculating the brightness temperature values, the dielectric permittivity values of the biological object tissues, which determine the attenuation of electromagnetic wave propagation, are taken into account and determine the depth of measurement.

Tissues with low water content are characterized by low dielectric permittivity and minor radiation power losses. In this context, brain membranes, flat skull bones, periosteum and aponeurosis are conventionally considered to be «radio-transparent» tissues that distort the recorded signals to the least extent.

Tissues with high water content, such as blood, muscle tissue, internal organs, skin, and brain matter, are characterized by high values of dielectric permittivity and signal attenuation [29].

Radiation propagation in biological tissues depends on its frequency. In particular, the depth of temperature measurement of internal tissues in the centimeter range of about 3 GHz reaches 5–7 centimeters. Measurement accuracy, tested against implanted thermosensors, is $\pm 0.2^{\circ}$ C [30].

Performing RTM with an antenna of about 30 mm in diameter allows to register EMR in a tissue volume reaching 1500 1800 mm³, and the calculated temperature values correspond to the average temperature in the whole volume. Implanted thermosensors provide information about the temperature in a much smaller volume of tissue, which seems to underlie the above discrepancies in results.

In modern computerized instruments, such as RTM-01-RES (OOO RTM-Diagnostics, Russia), the brightness temperature is automatically calculated based on the numerical solution of Maxwell's equation [31]. The measurement procedure is quite simple. The antenna is installed by pressing it firmly against the skin surface in the projection of the target tissue or organ. The measurement takes 3–5 seconds and the data is displayed in °C. The position of the antenna can be changed successively, so that measurements can be made in specific areas and a profile of the internal temperature distribution can be obtained within the resolution.

The RTM as a diagnostic and research tool is becoming increasingly popular in the study of brain temperature [32, 33], as well as in various conditions manifested by increased heat production [34]. In particular, RTM technology has been successfully used in the diagnosis of breast cancer and other malignant neoplasms [28].

Since inflammation is one of the key links in the onset, development and progression of atherosclerosis, the use of RTM allows the detection of high temperature heterogeneity in affected carotid arteries [35, 36]. Increased heat production in the inflammatory focus of pyelonephritis, kidney stone disease and inflammatory prostate disease can be detected by RTM [37, 38]. The RTM can be used for early diagnosis and monitoring of various inflammatory conditions [39], including pneumonia in COVID-19 [40]. Correlation between pain level and RTM results has been observed in the diagnosis of joint and muscle diseases, musculoskeletal disorders, and headache in degenerative disc disease of the cervical spine [41, 42].

The use of RTM showed that under normal conditions and at rest, the cortical temperature is lower than the basal temperature, while during physical activity it increases and exceeds the axial temperature by 0.3–1.0°C. After mild traumatic brain injury (TBI) in competitive boxers, focal hyperthermia with the temperature of 37.5–39°C was registered [43].

Patterns of EMR wave attenuation in tissues limit the resolution of the method when recording brain temperature, allowing only to estimate the temperature of the cortex of the cerebral hemisphere.

The Regulation of Brain Thermal Balance

Brain temperature is largely determined by the core temperature level, but the mechanisms of cerebral thermoregulation have specific features that distinguish them from regulation in other organs of the body heat center. High levels of heat production and limited passive ways of heat elimination provide conditions for heat accumulation in the brain, which is especially evident in physical hyperthermia, fever and brain diseases [44, 45].

The brain mass is about 2% of the adult body weight, while its contribution to the total body heat production reaches 20% in the normal resting state [7]. Basic cerebral metabolism is provided by the consumption of almost 20% of total glucose, oxygen and cardiac output [46].

Cerebral blood flow is heterogeneous: to adequately supply gray matter, approximately 80 ml of blood per 100 g/min is required, while white matter requires about 20 mL/100 g/min, with an average hemodynamic supply of the entire brain of 50–65 mL/100 g/min. In excitation, cerebral blood flow can increase significantly, reaching

140 ml/100 g/min, which supports the growing demand for oxygen and substrates, as well as the removal of excess metabolic heat [47].

The temperature of blood entering the brain is 0.2–0.3°C lower than in the aorta, and that of blood leaving the brain is 0.2–0.3°C higher [48]. The incoming blood is cooled by countercurrent heat exchange through dense contacts of the internal carotid arteries and the vessels of the jugular venous system, which collect blood cooled in the external environment from the mucous membranes of the upper respiratory tract and nasopharynx, as well as the skin of the head and neck. In addition, the emissary veins deliver cooled blood from the scalp to the dural sinuses directly to the brain surface [49]. This cools the surface of the cerebral cortex, protecting this universal «biological computer» from overheating.

Cerebral blood flow largely compensates for local heat release in some parts of the brain and enhances its accumulation in other parts [50, 51]. The heat release associated with excitation is a dynamic but rather inert process. The evoked temperature response to sensory stimulation develops at a frequency of approximately 0.005–0.008 Hz [52].

Any excitatory process that accompanies eating and sexual behavior, emotion, affect, pain, sensory stimulation, increases cerebral temperature, primarily of the cerebral cortex, and provides an increase in temperature heterogeneity [53]. Radial and interhemispheric gradients during stimulation can reach 1.5–2.5°C [54].

The use of implanted thermosensors in experiments revealed significant differences in cerebral and core temperatures, with the temperature of subcortical structures being 0.1–0.5°C higher than body temperature, with the highest values in the hippocampus [53, 55, 56]. According to proton NMR spectroscopy, the cortical temperature in healthy humans is lower than the temperature of the oral cavity, the tympanic membrane, and the skin over the temporal artery [57]. Comparing theoretical models with data from clinical and experimental studies, a clear dependence of heat release processes and heat accumulation on the intensity of local blood flow has been demonstrated [58].

In TBI, ischemic and hemorrhagic stroke, neurogenic fever commonly develops, which may be latent without changes in core temperature and worsens the prognosis and outcome of the disease [59–61]. In TBI, brain temperature is 1–3°C higher than core temperature [62].

The thermal response of the brain to injury is initiated by excitotoxic reactions and the development of local neurogenic inflammation. The release of proinflammatory cytokines at the site of injury affects the neurons of the hypothalamic thermoregulatory centers, providing a «set point» adjustment

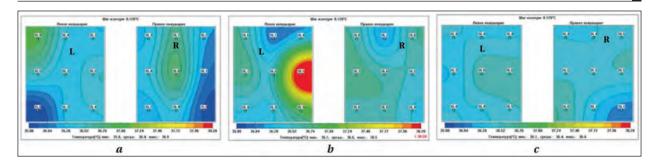


Figure. Examples of temperature distribution maps in the cortex of the left (L) and right (R) hemisphere of a healthy person at rest (a), a patient on the first day after an ischemic stroke (b) and a chronically critically ill patient (c) [69].

that tunes the body's thermostat to a higher level of regulation [63, 64].

Many factors are associated with the vulnerability of the brain's mechanisms for maintaining thermal homeostasis. The brain's nearly spherical shape favors heat accumulation, while its thermally isolated position in the skull prevents heat dissipation. The intensity of systemic and local blood flow is not determined by the increasing temperature, but rather by the internal demands associated with stimulation. In other words, the brain has no active thermoregulatory mechanisms. Pathways of passive cooling of the brain surface by blood flow through the emissary veins are unable to adequately compensate for the increase in heat production, and brain temperature does not affect the systemic circulatory responses involved in thermoregulation.

The structural, functional, and hemodynamic heterogeneity of the brain underlies its thermal heterogeneity, changes in which may indicate the development and severity of disease.

Brain Temperature Heterogeneity in Cerebral Disease

The use of proton NMR spectroscopy in cerebral infarction allowed the detection of an increase in temperature heterogeneity between the ischemic lesion and the contralateral intact regions [17]. Not only absolute temperature values, but also their diurnal variations, which are disrupted in stroke [65] and severe TBI [66], may have diagnostic relevance, as demonstrated by implanted thermosensors.

Daily fluctuations, temperature heterogeneity and its distribution over the brain surface can be studied using microwave RTM. In particular, RTM showed that healthy humans are characterized by a pronounced 24-hour circadian variation of cortical temperature with peaks at 12–16 hours and troughs at 0–6 hours. Correlation analysis revealed strong positive correlations between left and right hemisphere temperature changes, while moderate positive correlations were characteristic between diurnal variations of cortical and core temperature, emphasizing the relative independence of brain and

body temperature regulation [67]. In severe brain injury patients with chronic disorders of consciousness (CDC), such as vegetative state (VS) and minimally conscious state (MCS), the diurnal variations of cortical temperature were absent, apparently reflecting the gross lesions of cerebral structures, including central circadian oscillators [68].

In order to study temperature heterogeneity, a technique of sequential temperature registration in 9 symmetrical regions of the cortex of the large hemisphere on the left and right side (18 registration areas) was developed, which allows the construction of brain surface temperature distribution maps (Fig.) [69].

The studies were performed in healthy subjects at rest, in patients with acute ischemic stroke, and in patients with CDC after severe brain injury (VS and MCS) [70].

These studies showed that in healthy individuals resting cortical temperature is heterogeneous, with areas of relatively elevated (up to $36.7\text{--}37.4^{\circ}\text{C}$) and decreased (down to $35.8\text{--}36.3^{\circ}\text{C}$) values, while the average temperature of left and right hemispheres does not differ, averaging $36.4\text{--}36.7^{\circ}\text{C}$. The maximum difference between relatively warm and cold regions (ΔT) does not exceed $2.0\text{--}2.5^{\circ}\text{C}$, and their location varies individually and may be situation-specific.

In patients on the first day after ischemic stroke, regardless of the area of infarction, the average temperature of the right and left hemispheres increases to 37.9–38.0°C. At the same time, cerebral hyperthermia occurs in one third of patients with normal core temperature, i.e. it is latent. Focal hyperthermia develops with foci of increased temperature up to 39–41°C. The $\triangle T$ between «warm» and «cold» areas increases sharply, reflecting marked thermal heterogeneity. Patients whose $\triangle T$ was greater than 3–4°C died within 7–10 days. Thus, elevated brain temperature and severe thermal heterogeneity can be considered predictors of poor outcome [71].

The development of CDC after recovery from coma [72] is accompanied by a decrease in neuronal activity, metabolic disorders, and low hemodynamic

support of the brain. These processes may alter the cerebral thermal balance. In this category of patients, with values of averaged cortical temperature close to normal, $\triangle T$ seems to be less than 2°C, which indicates low thermal heterogeneity.

Correlation analysis between temperature values of symmetrical cortical areas of the left and right hemispheres in healthy subjects, patients with acute ischemic stroke, and those in CDC revealed significant differences. Thus, healthy subjects were characterized by positive significant medium strength correlations between symmetrical regions of the left and right hemispheres, with correlation coefficients (CC) ranging from 0.504 to 0.747.

In patients on day 1 of acute focal cerebral ischemia, the pattern of correlations between temperatures of symmetric brain cortical areas varied significantly. The CC varied widely from negative (–0.370) to positive (0.848) values, indicating an increase in interhemispheric temperature heterogeneity.

Correlation analysis of brain temperature relations in symmetrical regions of the large hemisphere cortex in patients with CDC showed that the CCs were in a narrow range from 0.971 to 0.947, reflecting the presence of strong positive correlations and uniformity of temperature distribution across the large hemisphere cortex.

According to the theory of functional biological systems developed by Pyotr Anokhin [73], the elements of an effectively functioning system are linked by medium strength connections, which provides enhanced opportunities for adaptation due to the variability of adaptive reactions generated by a set of system elements. The adaptive reserve of the system, when strong (rigid) links are established between its elements, is reduced by limiting the variability of reactions and strong interdependence, while extra strong impacts on the system and its components can lead to the rupture of links between them and cause system collapse. In turn, weakening and changing the direction of interrelations between the elements of the system cause its destruction, leading to the cessation of integrated activity.

Excessive increase of interhemispheric thermal heterogeneity and, on the contrary, its decrease, demonstrating disturbed connections between elements of the system, in this case between symmetrical regions of the cortex of the large hemispheres, accompany severe brain injuries and conditions of decreased consciousness, which proved to be characteristic for acute ischemic stroke and post-coma chronic disorders of consciousness.

The characteristic pattern of changes in temperature heterogeneity is also observed in psychiatric patients. In particular, in patients with schizophrenia, low cortical temperature heterogeneity was associated with an increase in the activity of inflammatory

blood markers and, in most cases, with a positive response of the patients to therapy. High cortical temperature heterogeneity appeared to be characteristic of patients with a deficient inflammatory proteolytic system and high levels of anti-brain antibodies. In these patients, the disease was more severe and resistance to therapy was observed in most cases [74]. Positive treatment results in patients with schizophrenia, acute focal cerebral ischemia and CDC were associated with an increase in decreased and a decrease in increased cortical temperature heterogeneity, respectively.

Despite a long history of research, the specific features of temperature homeostasis regulation remain largely unexplored. Recent data show that the temperature of subcortical brain structures can vary within a wide range in healthy individuals and in patients with TBI, and that both absolute values and circadian fluctuations of brain temperature are of diagnostic value, with abnormal diurnal changes being predictive of a significant increase in the probability of death in patients with severe TBI [75].

The pathogenetic role of cerebral hyperthermia, as well as the frequent occurrence of latent neurogenic fever, emphasize the importance of thermometry in the diagnosis, progression, and prediction of outcome of severe brain disease, with microwave RTM being the most convenient, simple, safe, and informative technique.

Moreover, the increase or decrease in temperature heterogeneity observed in severe brain injury may both be associated with the development of diseases and underlie the mechanisms of disturbed relationships between elements in the global systems of central regulation. This suggests that a reduction in the increased thermal heterogeneity or an increase in the decreased thermal heterogeneity may improve clinical outcome. The suggestion is supported by clinical observations showing that selective cooling of the brain helps to reduce the neurological deficit, mainly due to an increase in awareness, by controlling the thermal balance and reducing thermal heterogeneity in patients with acute ischemic stroke [76].

Conclusion

The RTM technology may be a helpful tool in the diagnosis of various brain disorders, including acute and chronic cerebrovascular disease and brain injury, psychiatric and neurological conditions, decreased consciousness and cognitive function.

Microwave RTM is a relatively new method of non-invasive deep tissue temperature assessment that has been used primarily for scientific purposes. However, the accumulated experience allows a prospective evaluation of its diagnostic performance, which definitely requires additional in-depth clinical and pathophysiological studies.

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