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THEORETICAL ANALYSIS OF THERMAL PROCESSES IN LIVING BIOLOGICAL TISSUE UNDER LOCAL HYPERTHERMIA TREATMENT. 1. BIOTHERMAL EQUATION AND LOCAL HYPERTHERMIA

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The authors provide the state-of-the-art of theoretical studies concerned with local hyperthermia.

Introduction. Heat transfer processes in a living organism have constantly attracted great interest. The emergence of hyperthermia (HT) – an effective method of cancer treatment – has sparked interest even more. By now a number of monographs [1–3] and surveys [4–9] have been published on this problem. For successful hyperthermia treatment a definite temperature (~43.5°C) must be maintained in a tumor during the treatment period. Further superheating is dangerous for an organism; at temperatures below 42°C the procedure is often ineffective or even yields a reverse effect [10]. Therefore reliable prediction of the thermal regime is the primary goal in theoretical HT studies. Although there are a large number of works on this problem [7–25 and others] it is still far from being explored thoroughly, and the control of temperature fields (invasive in the main) is an important part of thermal therapy.

Recently, methods of parametric control of HT based on use of a biothermal equation (BTE) have been successfully developed. Among those is perfusion determination by washout, i.e., the thermal washout method (TWM) [26–30]. A change of blood flow in an HT process is one of the important governing factors that also points to the efficiency of the treatment. The TWM allows one to continuously follow the changes of a blood flow in normal and malignant tissues. Requiring no additional equipment or special injections, the TWM is finding increasing use in clinical practice. At the same time the theoretical principles of the TWM are far short of correctness and need special analysis. Some works devoted to this problem point to different restrictions for TWM use.

Biothermal Equation and Its Modifications. The specific features of heat transfer in living tissue are due, first of all, to the great number of vessels and the continuous blood circulation. Just the variety of descriptions of convective heat transfer by blood leads to different modifications of the biothermal equation. In the general form, a change in temperature in a small tissue volume δV (at mass constancy in it) is written in the form

$$\int_{\delta V} c\rho \frac{\partial T}{\partial \tau} dV = \int_S \lambda \nabla T dS + \int_{\delta V} (Q_b + Q_m + Q_s)\, \delta V. \tag{1}$$

Though living tissue is heterogeneous, blood flow is often assumed to be homogeneous and isotropic within the limits of an isolated volume of biological tissue and is characterized by a single specific quantity, namely, perfusion W, i.e., blood flow based on some volume of living biological tissue. The blood flow rate per volume δV constitutes $W\delta V$. The blood that enters biological tissue has the arterial temperature T_a while the outflowing blood has the temperature of the tissue site T. Then convective heat transfer is

$$Q_b = \rho_b c_b W (T_a - T) \tag{2}$$

and the BTE (1) becomes (in differential form)

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$$c\rho \frac{\partial T}{\partial \tau} = \nabla (\lambda \nabla T) + \rho_b c_b W (T_a - T) + Q_m + Q_s . \quad (3)$$

The biothermal equation in form (1), (2) was suggested by H. Pennes in 1948 [31]. Naturally it does not take into account heat transfer near large vessels, nonisotropic perfusion, and some other effects. The validity of (3) near internal and external boundaries, where isotropy is infringed, and for relatively small volumes is doubtful.

The role of individual vessels in heat transfer and the nonisotropy of perfusion were investigated by M. Chen and K. Holmes [32]. They used the notion of an equivalent vessel length, i.e., a distance at which thermal balance between a liquid in a vessel and a surrounding tissue was attained. For small vessels, i.e., arterioles, venules, and capillaries, this distance is 2–3 orders of magnitude less than their characteristic length, and therefore the blood temperature in such vessels is practically equal to the temperature of the surrounding tissues. For macrovessels with a diameter >1 mm the equivalent length is 10–500-fold larger than their actual length, and therefore the blood temperature in arteries of such size is practically the same and equal to the rectal temperature. The main portion of heat is transferred by arterial vessels with a diameter of 0.2–0.5 mm and a length of about 10 mm. The latter dimension determines the bounds of applicability of Eq. (2) for describing convective heat transfer. The BTE of Chen is

$$c\rho \frac{\partial T}{\partial \tau} = \nabla (\lambda \nabla T) + \rho_b c_b W (T_a - T) + Q_m + \rho c \nabla T + \nabla (k \nabla T) . \quad (4)$$

The last two additional terms describe the nonisotropy of perfusion and the "extra" heat conduction associated with heat transfer between tissue sites by means of fine blood vessels.

The approach developed in [32] has exerted an influence on further investigations in this field. In some published works [33, 34] other BTE modifications are reported that take into account changes in the blood temperature in vessels, heat transfer between arterial and venous vessels, etc. In [11] the "extra" heat conduction is taken into account in a numerical analysis of local hyperthermia. A. Milligan [35] has modified the BTE to make the thermal washout procedure more precise.

An attempt to describe local thermoregulation of a biological tissue on the level of a microcirculation channel is undertaken in [36]. The blood system is represented as a hierarchy of vessels of the 1st, 2nd, etc., levels. On the level of a biological tissue site the temperature is self-regulated in some interval ΔT. An analysis has yielded the following equation to describe the change in the tissue perfusion:

$$\nabla \left(\frac{a}{ZW} \nabla W \right) - W_0 + W [1 - (T - T_a)/\Delta T] = 0 , \quad (5)$$

where $a = \lambda/(\rho c)$ is the thermal diffusivity of the tissues; Z is a dimensionless parameter (equal to 2–3); W_0 is the blood circulation rate at the temperature $T = T_a$. Expression (5) together with the BTE (3) specifies a system of equations for the temperature fields and the blood circulation rate. The authors of [36] do not give solutions of these equations; however, this system of equations is reduced, as can easily be checked using characteristic scales larger than $X = \sqrt{aW}$, to Chen's BTE (4) with the "extra" heat conduction linearly dependent on the temperature.

However, in the majority of applications the classical Pennes BTE (3) is used because of uncertainty of the equation parameters and, first of all, insufficient knowledge of the blood flow. This does not allow an unambiguous choice of any modification to be made. At the same time the Pennes approach, based on general integral relations, seems to be sufficiently sound.

Perfusion, Its Distinctive Features and Role in Heat Transfer Processes. Among the BTE parameters the blood circulation rate is especially important. Its integral characteristic, namely, perfusion, underlies the vital activity of organisms and plays a dominant part in a heat transfer process. At present a great deal of information has been gained about the perfusion of individual organs and tissues under normal and extremal conditions, different pathologies, and the action of drugs [37, 38]. It is found that perfusion changes substantially under the action of different factors.

For heat transfer involving hyperthermia the response of the blood flow to thermal stress plays a special part. In [6, 21, 39–47] the effect of temperature on the perfusion in normal tissues is investigated. Attempts to generalize the results obtained and use the BTE encounter some difficulties. First, perfusion data are based on

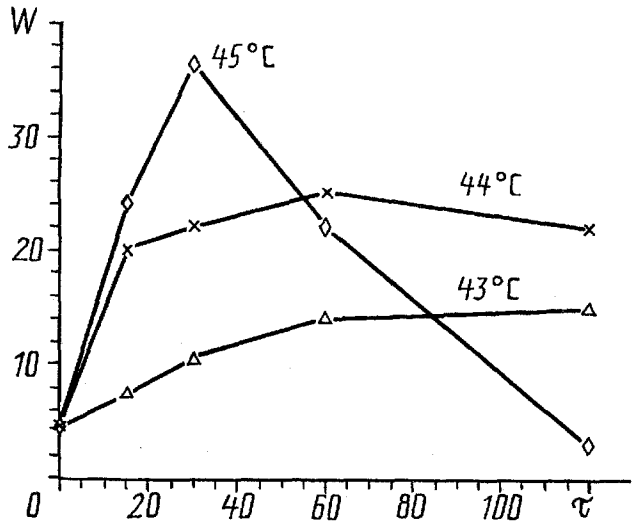

Fig. 1. Muscle blood flow in the lower extremities of rats versus heating time in a water bath at different temperatures [44]. W, ml/(100 g·min); τ, min.

different methods of heating (local or total), and the temperature is not always controlled sufficiently precisely. Second, the blood flow has been determined by different methods that are not always compatible and have different time resolution. Finally, measurement data refer to different animals, patients, or sites of a body or organ.

Perfusion rates have been determined by three main methods, namely, propagation of isotopes or other substances [6, 21, 39, 41, 43, 44], the thermal washout method [40, 42], or use of a laser Doppler flow meter [45–47]. The first method is traditional and well-known but its time resolution is not better than 15 min; moreover, this method is difficult to use for monitoring perfusion rates.

In [44] data are reported on muscular and tissual blood flows in the lower extremities of rats upon local hyperthermia in a water bath (42–45°C) obtained by the last method. According to [44], the blood flow at 45°C undergoes an approximately 15-fold increase for skin and an 8-fold increase for muscular tissue. It is characteristic that on heating up to 44°C or more the blood flow at first increases and then abruptly decreases. At a higher temperature the time for attaining a maximum is shorter and the maximum itself is higher (Fig. 1). The authors of [44] give the following explanation for the discovered effects. Tissue heating favors the formation of vasoactive substances (bradikinin, histamine, etc.), which enhance perfusion. An increase in the blood viscosity leads to stasis (the minimum permissible perfusion) due to, as believed, hematocrit enhancement.

A detailed study of the effect of temperature on the perfusion of muscular tissues of the upper and lower extremities of dogs is made in [40]. Unlike [44], there local SHF hyperthermia (2450 MHz) has been used. For experiments, 15 large mongrels with a mean weight of about 25 kg were taken. Sites of 7×4 cm^2 were exposed to irradiation; the temperature was recorded by 18 thermocouples. Prior to irradiation all the animals were anesthetized (sodium pertobarbital, 60 mg/kg). Measurements were made by the TWM, for which the source was switched off for 2 min every 5 min. Measurements were made at a depth of 1 cm at the temperatures 43, 45, and 47°C. In all the cases the blood flow increased and then decreased. The maximum perfusion W_m depended on the temperature as follows:

$$W_m = W_0 \exp(0.372\,(T - 37.0)), \tag{6}$$

where $W_0 = 3.15$ ml/(min·100 g) is the perfusion at 37°C; T is the maximum temperature. The time τ_m for attaining the maximum is determined by the expression

$$\tau_m = \tau_0 \exp(-0.187\,(T - 37)), \tag{7}$$

where $\tau_0 = 11.7$ min. No explanations for the revealed regularities are reported in [40].

An extraordinary response of the normal tissues of the dog's extremities to local SHF heating is reported by the authors of [42]. An interesting effect of temperature fluctuations in a muscular tissue at a constant source

power has been observed. The amplitude of these fluctuations attained 7°C, the period lasted 60–30 min. Such a reaction of the tissues is due to changes in the local blood flow, which responds to temperature changes with some delay.

In [45, 46] the effect of hyperthermia on blood flow in human skin is investigated. For this, a laser Doppler flow meter was used.

In [45] the impact of heat (40°C) and cold (5°C) on the skin perfusion of 16 patients was investigated. On heating, the blood circulation rate attained its maximum approximately 20 min after the beginning of heating and increased 2.7-fold. The blood volume attained its maximum after 40–50 min (4.5 times the initial volume). The total increase amounted to $4.5 \times 2.7 = 12$. It was found that the blood flow increased drastically during the first 2 min of heating as well as immediately after completion of heating. Such abrupt increases are explained as follows. When the capillaries become engaged and vasolidation occurs due to a sudden increase in the skin temperature, the reflectory reaction or the self-regulation mechanism can cause vasoconstruction or subsequent weakening of blood circulation.

A decrease in the blood circulation rate after a 30–40 min increase [47] has been noted by many authors although no adequate explanation for it is available at present.

The role of the nerve factor in the response of skin perfusion to heating is debatable. It is most likely that a change in the capillary blood circulation is caused by a local axon reflex from hypodermic receptors to vessels as a direct consequence of heating. The humoral factor may also exert some influence.

In [46], a logical continuation of [45], the change in the skin perfusion of 16 patients has been investigated at the temperatures 35°C, 37, 40, 41, 42, and 43°C. The measurements have confirmed the data of [35]. A maximum was observed after 30–40 min of heating. At 43°C the blood circulation did not weaken. An abrupt change in the skin temperature resulted in drastic enhancement of blood circulation. In the temperature range 37–43°C the maximum blood circulation increased linearly with the temperature.

The authors of [45, 46] did not take into consideration the important fact that the dependences of the blood circulation rate and the blood volume are strongly correlated with each other. Consequentely, variations of these dependences were caused by vasodilation and vasoconstriction.

The blood flow in tumors has been studied by many investigators [6, 17, 21, 35, 43, 44, 48–55]. In [45, 48] emphasis is given to the change in the blood flow due to hyperthermia, i.e., to the therapeutic effect. We are interested in another side of the problem, i.e., in the change in the blood flow due to heating.

The blood system in a tumor differs substantially from the vessel system of normal tussues and, according to [44], contains:

a) capillary sprounts;

b) sinusoidal vessels with intermittent endothelial lines;

c) blood channels without ordered endothelial lines;

d) giant capillaries;

e) matured capillaries with basilar membranes;

f) host vessels.

At the beginning of tumor growth it is fed by host arteries. The number of host arteries hardly increases during tumor growth, while the amount and length of tumor capillaries fed by the same arteries increase. This leads to a decrease in the arterial pressure. At the same time the extravascular pressure increases as a consequence of tumor growth in a constricted space. This is likely to be a reason for the necrosis of the central part of the tumor.

According to [44], at the normal temperature the tumor blood flow is, as a rule, weaker than in the surrounding tissues although this is not always the case. On heating, the tumor perfusion increases insignificantly and then decreases.

Using numerous data [43], the perfusion in unheated tumors may be represented as a function of the weight m (g) as

$$\log (W) = -0.1721 (\log m)^2 - 0.5382 (\log m) + 1.4745 . \quad (8)$$

For heating of tumor to 43°C for 1 h relation (8) is modified to the form

$$\log (W) = -0.1290 (\log m)^2 - 0.5414 (\log m) + 1.4718 , \quad (9)$$

although the differences are statistically insignificant. Expressions (8) and (9) show a substantially smaller blood flow in large tumors, which is confirmed, in fact, by all authors.

In [21] the volume velocity of the blood flow Q in the carcinoma $W256$ is shown to depend on the tumor size as

$$Q = am^{-2/3} \ \text{cm}^2/(\text{g}\cdot\text{h}) , \quad (10)$$

where m is the tumor mass, g; $a = 26 \ \text{cm}^3/(\text{g}^{1/3}\cdot\text{h}^{-1})$. Data on the blood flow in a lymphosarcoma are described by the relation

$$Q = Q_0 + b\xi^2 \ \text{cm}^3/(\text{g}\cdot\text{h}) , \quad (11)$$

where $Q_0 = 72 \ \text{cm}^3/(\text{g}\cdot\text{h})$, $b = 908 \ \text{cm}^3/(\text{g}\cdot\text{h})$, $\xi = r/R$, r and R are the distance from the tumor center and its radius.

In [52–54] practically no stasis was observed in tumor vessels. This difference from the results obtained by other investigators is associated, in the author's opinion [52], with a different response of human tumors [52–54] and implanted tumors of rodents [43]. A two-three-fold increase in perfusion during hyperthermia treatment was observed in the majority of cases and occurred during the first 10–20 min of heating. Subsequently, the blood flow did not change, as a rule. Also, no statistically significant dependence on the heating temperature was observed. Perhaps, this is due to the different initial blood flows in tumors and insufficient statistics.

Summarizing the experimental data on the response of perfusion of tissues to heating it should be noted that:

1. Perfusion in a locally heated biological tissue changes as a function of the heating temperature and its duration. For many kinds of normal and tumor tissues under isothermal conditions the perfusion at first increases due to vasodilation and then decreases due, probably, to rheological factors.

2. The responses of blood flows in normal and tumor tissues to local heating are highly different with respect to the degree of perfusion modification. The perfusion in normal tissues under local hyperthermia treatment increases by an order or more, while the blood flow in a tumour usually undergoes enhancement by no more than a factor of 2–3.

BTE and Perfusion Models Applied for Prediction of the Local Hyperthermia Regimes and Parameters. Predictive evaluation of hyperthermia is one of the important problems of theoretical studies. As mentioned above, either the BTE (3) or its modifications serve as a basis for theoretical analysis of thermal fields. Depending on the goals of the investigations, one-dimensional [11, 12, 15, 16, 19, 28], two-dimensional [10, 14, 18, 20], or three-dimensional [24, 25] problems have been adopted in different calculations. One-dimensional approaches have been employed, as a rule, to reveal the role and the influence of different factors, and multidimensional ones for a more detailed prediction of the thermal fields.

A theoretical analysis of local SHF hypothermia consists of two stages: calculations of the specific absorption of electromagnetic energy as a function of the source configuration and its location, the radiation frequency, the geometric size and composition of tissues, etc. [13, 15, 56] and calculation of the temperature field based on the BTE solution and the results of the 1st stage [7, 13, 57, etc.].

A theoretical analysis of the temperature fields in SHF hyperthermia represents a separate and rather difficult problem. The relative contribution of different factors to heat transfer processes is discussed in [13, 17, 21, 27, 30, 57]. In [13, 17, 21] the role of heat conduction, perfusion, and metabolism for different boundary conditions is analyzed in detail. The influence of the geometry and composition of tissues is investigated in [17, 21, 57].

In a theoretical analysis it is most difficult to account perfusion of tissues. Four groups of approaches may be singled out.

1. The blood circulation rate does not change on heating and depends only on the kind of tissues [24, 27–30]. In the majority of these investigations the role of different factors, the geometric characteristics of the

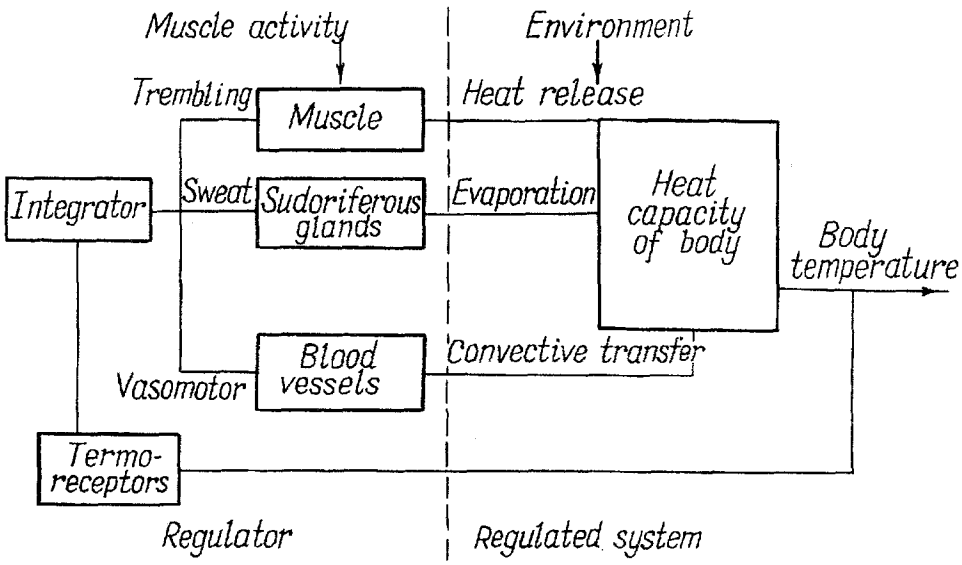

Fig. 2. Simplified block diagram of a human control thermal-regulation system [63].

emitter, etc. are analyzed. These models do not take into consideration the change in the perfusion and give a very rough picture of the temperature fields in local hyperthermia.

2. The blood circulation rate is a function of the local instantaneous temperature [11, 16, 19]. These more realistic models allow, in a first approximation, changes in the perfusion during heating to be taken into account. For this, use is made of different dependences of the blood circulation rate on the temperature. In [16] the blood circulation rate in a muscle is shown to change proportionally to the metabolisn of the tissues according to the Q_{10} law:

$$W = W_0 \, 2^{(0.1\Delta T)} . \tag{12}$$

However, this dependence does not correspond to experimental data; the increase in the blood circulation rate upon heating is usually more substantial than the corresponding change in the metabolism rates. In [11] a linear dependence of the blood circulation rate on the temperature, based on experimental data [39], is used in the form

$$W = W_0 \, [1 + a \, (T - 37^{\circ}\mathrm{C})] \quad \text{at} \quad T > 37^{\circ}\mathrm{C} , \tag{13}$$

In [19] the following relations for perfusion are used:

$$W = W_0 \left\{ 1 + a_1 + a_1 \, \mathrm{th} \, [b \, (T - 39)] \right\} \quad \text{at} \quad T < 39 , \tag{14}$$

$$W = W_0 \left\{ 1 + a_1 + (a_2 - a_1) \, \mathrm{th} \, [b \, (T - 39)] \right\} \quad \text{at} \quad T > 39 , \tag{15}$$

where for a normal tissue $a_1 = 0.2$, $a_2 = 0.4$ and for a tumor $a_1 = 0.2$, $a_2 = -0.4$. For muscle W_m and skin W_s perfusion the following relations are used in [16]:

$$W_m = W_{m0} \exp \, [0.0953 \, (T - 37)] , \quad W_s = W_{s0} \, [1 - 0.8 \, (T - 37)] . \tag{16}$$

The variety of the dependences used to describe blood flow modifications under hyperthermia treatment reflects, to a certain degree, the large scatter in empirical data (see above).

Although the works described above represent some progress in improvement of the hyperthermia model, it is insufficient to use just the instantaneous temperature dependence to describe the regularities in the change in the perfusion during heating. Experimental studies of the blood flow velocity (see above) show that the perfusion intensity changes with time even when the prescribed temperature of the tissues has been attained.

3. Thermal regulation models [58–62], dictated by the needs of space medicine, aquanautics, etc. have been actively developed in the 60–70s. Recently attempts have been made to use thermal regulation models for analysis of the thermal fields in hyperthermia treatment [25, 63].

A typical example of a thermal regulation model is the Stolwijk model [63], in which the blood flow represents a sum of two components: passive, proportional to the metabolism and described by relation (12), and active, not related to metabolism (Fig. 2). The active component of the blood flow is a function of the afferent signal of the central thermoregulation system, which sums up the signals of skin thermoreceptors as well as those of the brain. The output (efferent) signal is distributed with respect to different parts of the body according to certain weight coefficients and includes skin cooling due to sweating (thermal actions), enhancement of metabolism in tissues upon cooling, and changes in the active part of the blood flow under both kinds of action simultaneously). Thus, in thermal regulation models the blood flow velocity depends on some integral temperature and some integral temperature changes.

Undoubtedly, for prediction of general or regional hyperthermia this type of models is advantageous over the traditional approach, which does not account for the thermal regulation of the organism. At the same time such models do not take into consideration local thermal regulation in local heating, and therefore they will be ineffective for the analysis of local hyperthermia.

4. In adaptive models [10, 18, 23, 63], the blood flow velocity is not prescribed a priori but is calculated from the condition of the best correspondence of theoretical to experimental temperature data. The use of such models is limited to operative prediction of the temperature fields and retrospective analysis of hyperthermia.

Use of the BTE for Control of Perfusion in Hyperthermia Treatment. Recently methods for determining perfusion have been successfully developed. Among them is the aforementioned TWM (in the foreign literature in addition to thermal washout the term "thermal dilution method" is used) [28]. It consists in the following. With the source being off, $Q_s = 0$, the BTE is written in the form

$$c\rho \frac{\partial T}{\partial \tau} = \nabla (\lambda \nabla T) + \rho_b c_b W (T_a - T) + Q_m . \tag{17}$$

At a sufficiently high temperature convective heat transfer greatly exceeds transfer by conduction [27], tissue metabolism also becomes comparatively weak, as compared to heat transfer by blood, and (17) acquires the form

$$c\rho \frac{\partial T}{\partial \tau} = \rho_b c_b W (T_a - T) . \tag{18}$$

Equation (17) is readily solved when $W = \text{const}$, $\rho_b c_b \approx \rho c$:

$$T = (T_1 - T_a) \exp (- W\tau) + T_a , \tag{19}$$

whence

$$W = \frac{1}{\tau_1 - \tau} \ln \frac{T - T_a}{T_1 - T_a} . \tag{20}$$

The TWM in form of (19) was used in [26], apparently, for the first time, and subsequently has found wide application for various investigations.

Expression (20), derived from an approximate BTE, determines some effective velocity of the blood flow. But, as shown in [52–54], the values obtained by this method correlate with the therapeutic effect in hyperthermia; therefore, the method may be used for thermal dosimetry.

On the other hand, neglect of heat conduction is not always justified. In [29] the role of heat conduction was investigated with the aid of a one-dimensional model. The effective perfusion calculated by the TWM may differ, as was shown, from the actual perfusion by a factor of 2 or more. A similar analysis has also been made in [30]. A. Milligan [40] has introduced special empirical coefficients that make it possible to reduce TWM data to the actual perfusion. These coefficients are a result of processing the temperature curves; however, the large scatter of the values obtained shows that simultaneous determination of perfusion and the effective coefficient from the same data is not justified.

A thorough study of the TWM based on the Green function of (17) at $Q_m = 0$ was conducted in [28]. In particular, it is shown that the error in determining the perfusion increases sharply near the boundaries, especially in the case of a boundary condition of the first kind (strong cooling of the skin surface) as well as of relatively low

perfusion (less than 20 ml/(100 g·min)). In other cases TWM data correspond to the actual perfusion with an accuracy no worse than 20%.

Unfortunately, in the cited works concerned with the applicability of the method it has been assumed that the perfusion does not change within a measurement interval. But this interval usually comprises 1–5 min, and the temperature of a biological tissue may decrease by several degrees, thus causing a change in the actual perfusion and affecting the measurement quality.

Another method used to determine the blood flow velocity in hyperthermia treatment is the stationary-state method [29]. If the temperature of the biological tissue site is stabilized during hyperthermia treatment, then the BTE acquires the form

$$0 = \nabla (\lambda \nabla T) + \rho_b c_b W (T_a - T) + Q_s . \tag{21}$$

Neglecting, as before, heat conduction and metabolism, we arrive at

$$W = \frac{Q_s}{\rho_b c_b (T - T_a)} . \tag{22}$$

Unlike the TWM, determination of perfusion by the stationary-state method requires knowledge of the specific absorption of the radiation (heat release) (SAR) on the given site of the biological tissue, which is not always known. Moreover, the SAR is often determined by relation (22) while using other procedures for perfusion determination. If the SAR is determined independently, e.g., by measurements on phantoms, then (22) serves as a reliable tool for measurement of the effective perfusion.

A more general approach, combining both methods, is shown in [42, 57]. With neglect of heat conduction and metabolism, the BTE may be written as

$$c\rho \frac{\partial T}{\partial \tau} = \rho_b c_b W (T_a - T) + Q_s (\tau) , \tag{23}$$

whence

$$W (\tau) = \frac{Q_s - c\rho \dfrac{dT}{d\tau}}{\rho_b c_b W (T - T_a)} . \tag{24}$$

Before heating, the tissue temperature is constant so that heat sinks and sources are counterbalanced, and therefore in the initial period of heating the specific absorption in the tissue is determined by the formula

$$Q_s (0) = c\rho \frac{dT}{d\tau}\Big|_{\tau=0} . \tag{25}$$

At subsequent moments of time Q_s may easily be calculated bearing in mind that it is proportional to the incident power P [29]:

$$Q_s (\tau) = Q_s (0)\, P (\tau)/P (0) . \tag{26}$$

Thus, this method makes it possible to determine and continuously trace the perfusion at a given point of the tissue by using the known $T(\tau)$ and $P(\tau)$ dependences. In particular, when $P = 0$, we obtain formulas for the TWM. As in the case of the TWM, we mean, naturally, determination of some effective perfusion that is close to the actual one under certain conditions.

Rheological Factors. It is quite evident that the blood rheology exerts an influence on perfusion and through it on the space-time evolution of the temperature fields in biological tissue. It is known that on passing to pre- and postcapillaries the viscosity may change several tenfold [64]. Moreover, a strong influence is exerted by the plastic component of the flow, associated with structure formation in the blood, which becomes stronger in almost any pathology. In principle, it is not difficult to take into account the blood rheology in large vessels. But it is rather difficult to relate the perfusion with the rheology. Such an attempt was made in [12], where the Karman–Cozeni ideas for liquid flow through a porous medium is used. From the requirement of equality of the flow rate and the pressure of an effective circular tube its diameter is determined. Then characteristics of the Casson viscoplastic

fluid flow are calculated that adequately describe the blood rheology. The obtained temperature fields in the biological tissue correlate fairly well with calculations of other authors [65]. Correct account for the blood rheology in the BTE is one of the fundamental problems in further research studies.

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NOTATION

ρ, c, density and heat capacity of the tissue, ρ_b, c_b, the same for blood; T, T_a, temperature of the tissue and arterial blood, respectively; λ, thermal conductivity; Q_m, heat of metabolism; Q_s, heat release due to an external source; Q_b, convective heat transfer by blood; W, volume velocity of blood flow; τ, time.

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