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THEORETICAL ANALYSIS OF THERMAL PROCESSES IN LIVING BIOLOGICAL TISSUE UNDER LOCAL HYPERTHERMIA. II. ANALYSIS OF TEMPERATURE FIELDS IN LOCAL SHF HYPERTHERMIA WITH REGARD FOR NONSTATIONARY NONLINEAR TISSUE PERFUSION

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A theoretical model of the kinetics of perfusion based on temperature-time superposition is suggested.

Introduction. The analysis of SHF hyperthermia includes several aspects: the comparative influence of different factors on hyperthermia; prediction of temperature fields for tissues under hyperthermia; effective hyperthermia control; a retrospective analysis of hyperthermia; and determination of heat doses and perfusion in a hyperthermia process [1, 2]. As a basis, a bioheat equation (BHE) is used that describes the heat release in living biological tissue due to metabolism and electromagnetic energy absorption as well as heat transfer by conduction and convection.

It is most difficult to account for the convective factor, which is related with perfusion and plays a decisive part in formation of temperature fields in hyperthermia. In [1], a survey is made of experimental studies of perfusion in normal and tumour tissues under hyperthermia conditions. It is established that during local heating perfusion in normal tissues substantially increases, sometimes by more than one order of magnitude. Therefore it is necessary to introduce some empirical temperature dependence of the perfusion rate into the BHE [3-5], which complicates the model. Another way to describe blood flow is by thermoregulatory models [6-8], in which the perfusion rate depends on some integral temperature and its integral changes. Though the mentioned works are a step to improve the hyperthermia model, it is insufficient to describe perfusion only by the instantaneous temperature dependence. Experimental studies of perfusion in normal tissues [9-13] show that the perfusion rate continues to change with time even when the preset tissue temperature is attained. Perfusion continues to increase up to some moment and then starts decreasing. Accounting of these regularities in a theoretical analysis of hyperthermia dynamics involves difficulties since the data obtained pertain to isothermal processes, they are diverse and inconvenient for parametrization. Overcoming these difficulties is one of the goals of the present work.

Proposed Mathematical Model. Heat transfer in a living body is determined, to a considerable extent, by perfusion. The latter depends on both the temperature and the exposure to heat, i.e., heating duration. An effort to take into consideration this factor in the BHE encounters certain difficulties. First of all, the experimental data pertain to isothermal processes while in the bioheat equation, the temperature is a variable and sought parameter. Generally speaking, correct solution of the problem requires a knowledge of the kinetics of change of the parameters of the vascular system under heating. However, in such a statement the problem is extremely difficult because the processes in the organism depend on many factors, whose interrelation is complicated and ambiguous.

In the mechanics of polymers [14] and in chemical kinetics [15], problems often arise in which isothermal measurement data are used to describe nonisothermal processes. If the kinetics of the processes is unknown, simplified methods including, first of all, the so-called method of temperature-time analogy (TTA) are employed. The essence of the latter lies in the fact that the time changes of the process are associated with its intensity, which

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is determined by temperature. Applicability of the method depends on two assumptions: that (a) the temperature dependence of the intensities of different processes must be one and the same ("one process") and (b) no structural changes occur in the system. Often it is impossible to prove or disprove these assumptions theoretically and therefore the applicability of the method is substantiated empirically. If we represent isothermal curves in the form of a logarithmic dependence on time, in the case of TTA validity the curves merge and form a single (universal) curve by displacing individual dependences along the x- and y-axes. Mathematically, the TTA for isothermal processes is written as follows

$$\alpha (T, \tau) = f_1 (T) \Phi [f_2 (T) \tau], \tag{1}$$

where $f_1(T)$ is a function that depends only on the temperature and type of material, and $\Phi(\xi)$ is the universal temperature-time dependence. The functions $f_1(T)$ and $f_2(T)$ in Eq. (1) are determined by the values of displacement and, naturally, must have a justified form. As a result of TTA application, changes in the parameters are represented as a function of reduced time, which substantially simplifies the representation of experimental curves.

Use of the TTA makes it possible to pass easily to nonisothermal processes. For this, we replace $\xi = f_2(T)\tau$ by

$$I = \int_0^{\tau} f_2 (T)\, d\tau . \tag{2}$$

For isothermal processes such a substitution is merely a formal procedure; for nonisothermal processes it is assumed in (2) that $T = T(\tau)$.

We now consider the possibility of using the TTA to describe approximately the kinetics of changing the blood flow upon heating. The majority of investigators distinguish two phases of blood-flow variation under heating: phase I, with enhanced blood flow; and phase II, which is accompanied by a drastic decrease of the microcirculation intensity. The cause of these phenomena is not quite clear from the physiological viewpoint: in [12], it is assumed that phase I is associated with the accumulation of vasoactive substances (bradikinin and histamine), whereas phase II involves a hematocrit increase due to enhancement of the increased permeability of vessels and, consequently, a drastic increase of the rheological factor due to increased blood viscosity and plasticity. Limiting blood flow weakening in a biological tissue is defined as stasis.

The blood-flow weakening highly depends on the temperature of the process. For instance, according to data of [16] heating by 1°C reduces by approximately half the time of attaining stasis in sarcoma BA 1112; the temperature-time relation for 50% microcirculation weakening τ_{ST50} in the temperature range 42.5–44.0°C is

$$\tau_{ST50} = \tau_0 \exp [- 0.747 (43 - T)], \tag{3}$$

Similar relations also hold for blood flow in normal tissues and are observed in many biological objects for both reversible and irreversible processes [16]. Thus, the temperature dependence of cell death *in vitro* [17] for a wide temperature range (43–57°C) obeys the same regularities. The same relations have been used in [4] to evaluate thermal dose.

The character of changes in the blood flow in phase I is, obviously, peculiar for various tissues since it is related to the thermoregulatory capacity of peripheral vascular systems. It is well known [12, 18] that the enhancement of blood flow in a tumour due to underdevelopment of its circulatory network is substantially weaker than in the host normal tissues. Apparently, the enhancement of blood flow is always restricted by some physiological limit that is different for some kinds of tissues. According to the data of [13] in the range of 37–43°C the maximum magnitude of skin linearily depended on temperature. Muscle blood flow in dog extremities has been found to depend exponentially on temperature [10]. Various tissues exhibit different rates of blood-flow enhancement. Thus, in phase I no universal temperature-time dependences are likely to hold. As is known [14], in the case of two processes with different temperature regularities the TTA approximation may be also used:

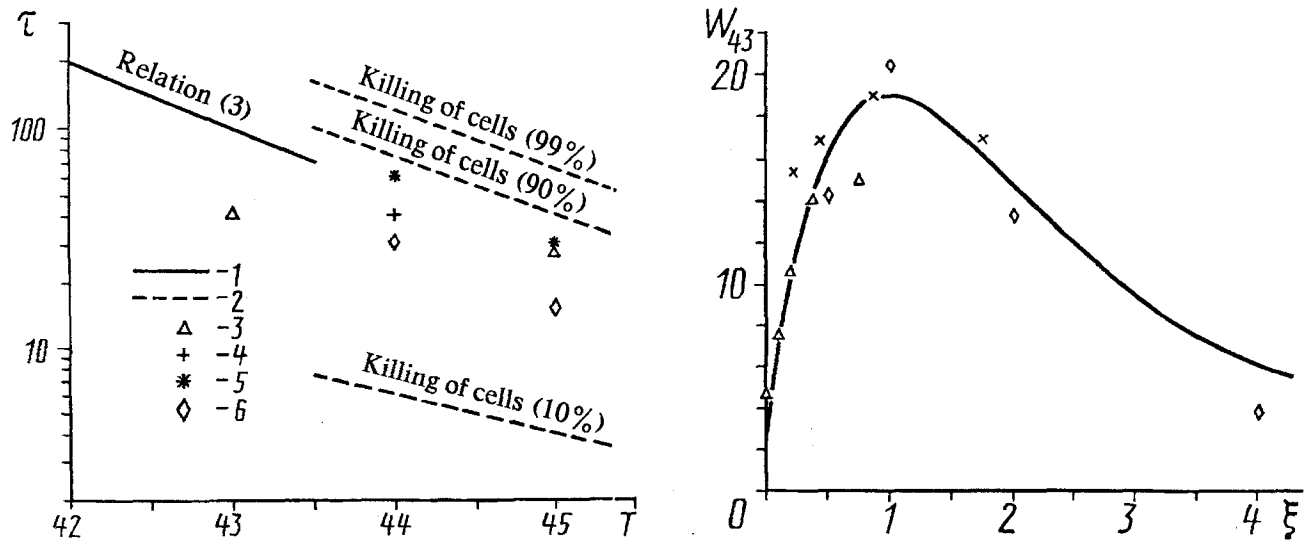

Fig. 1. Temperature-time characteristics of some biological processes in hyperthermia: 1) 50% weakening of microcirculation [16]; 2) isolines of the killing of cells [17]; 3) maxima of blood flow [10]; 4) maxima of muscle blood flow [11]; 5) maxima of skin blood flow [12]; 6) maxima of muscle blood flow [12]. τ; T, °C.

Fig. 2. Muscle perfusion rate of rats exposed to water bath heating at different temperatures [12] reduced to the universal dependence. W_{43}, perfusion rate reduced to 43°C, mm/(100 g·min). ξ, min.

a) in each region of the temperature-time diagram where one of the processes is dominant;

b) in the "equilibrium region" where two processes balance each other. In this case, the temperature coefficient differs from the coefficients of each process.

However, in the general case of two processes it is insufficient to use only isothermal data; it is necessary to conduct a special series of experiments, i.e., to measure the blood flow rate at different heating rates. A comparison of the perfusion rates with the data of isothermal measurements allows a final conclusion to be drawn that the TTA may be used to describe local hyperthermia.

Isothermal data also fail to describe stepwise changes in blood flow caused by abrupt changes of temperature [13]. To describe such a response and include it in the model, it is necessary to measure the blood flow rates at temperature jumps.

At sufficiently high temperatures, phase II distinctly manifests itself. The characteristic times of the process, i.e., the times of the onset of maximum perfusion will be determined by the temperature-time characteristics of phase II. Figure 1 shows the temperature-time characteristics of different biological processes in the temperature range of 42–45°C. As is seen, the times of attaining maximum perfusion [10, 12] correspond well to relation (3). The values of the maxima and their temperature dependences will be different for various tissues.

Thus, in a first approximation the perfusion rate W is determined by the product of two functions:

$$W = f_1(T)\,\Phi\,[f_2(T)\,\tau]. \tag{4}$$

Figure 1 in [1] and Fig. 2 of the present work show the time dependence of perfusion according to the data of [12] in the initial form and after reducing it to the universal temperature-time dependence. Remembering the complicated character of biological processes, this procedure may be considered quite successful. At $f_2 = \exp(-0.8\Delta T)$, $f_1 = \exp(0.7\Delta T)$ the perfusion curves merge and form a single curve (within the limits of measurement errors):

$$W - W_0 = f_1\,\Phi(\xi) = W_0 \exp(0{,}7\Delta T)\,\xi \exp(-\xi). \tag{5}$$

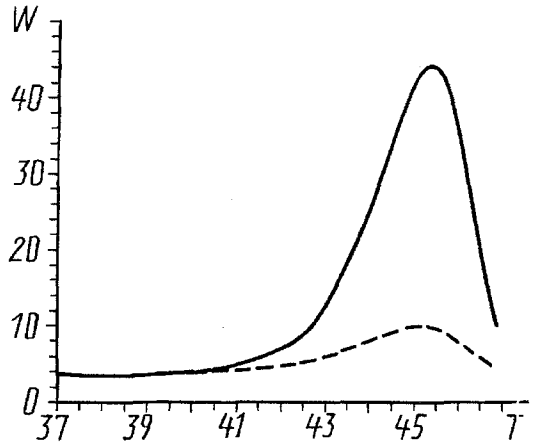

Fig. 3. Perfusion in the normal muscle tissue (solid line) and in tumour (dashed line) after 30 min heating according to relations (5) and (8). W, mm/(100 g·min).

If the perfusion curves are similar to each other and have one maximum at $\tau = \tau_m$, the time-reduction procedure may be simplified. Since τ_m is the only time characteristic of the curves, the dependence $\tau_m(T)$ determines the function $f_2(T)$:

$$f_2(T) = C/\tau_m, \tag{6}$$

where C is a numerical coefficient whose value is insignificant (in further calculations it is assumed equal to unity).

Thus, the proposed model is reduced to substitution of some dimensionless "physiological" time

$$\xi \to \int_0^\tau dt/t_m(T). \tag{7}$$

for the "physical" time τ.

As mentioned above, changes in perfusion are caused by the accumulation of physical and/or chemical changes in an organism, which is mathematically expressed by the integral, therefore use of expression (7) is quite justified.

Use of the notion of "physiological" time allows the experimental curves to be scaled in a natural manner.

Application of the Model for Describing the Typical Processes in Living Tissue. We shall consider a few several simple applications of the proposed model which allow some known experimental dependences and effects to be describe.

Temperature Dependence of the Perfusion Rate at the Described Heating Time. In [12], the authors summarize experimental data on the temperature dependence of perfusion in normal and tumour tissues upon 30-min heating. Our relation (5), obtained as a result of reducing the initial isothermal data on muscle perfusion, also allows one describe a similar dependence. To describe tumour perfusion W_{tum}, we shall use a relation analogous to (5):

$$W_{\text{tum}} - W_{0,\text{ tum}} = W_{0,\text{ tum}} \exp(0.1\Delta T)\, \xi \exp(-\xi). \tag{8}$$

The coefficient in (8) is such that the perfusion rate is doubled upon heating up to 43°C. A comparison of (5) and (8) with respect to temperature and the data of [12] shows a rather good fit of the curves (Fig. 3), which demonstrates the potentialities of the reduction method used.

Water Bath Heating. We shall consider a procedure of water bath heating of the lower extremities of rats at different water temperatures investigated experimentally in [12]. We write the bioheat equation in an axial symmetry approximation as

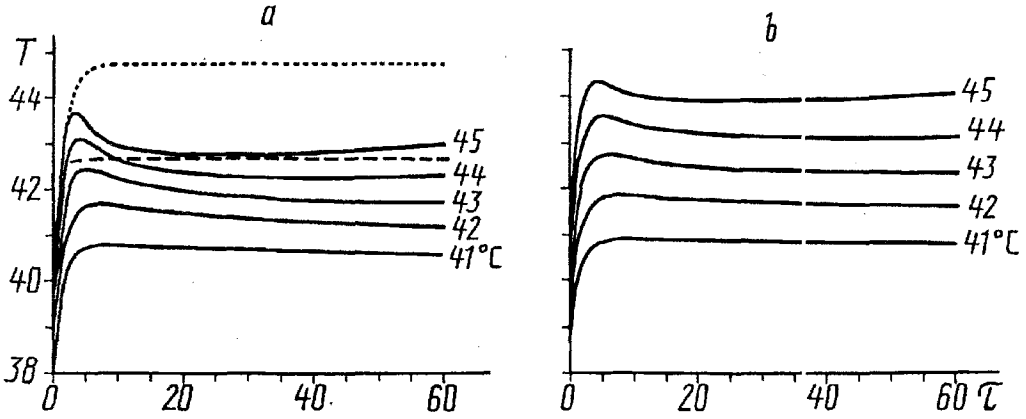

Fig. 4. Modeling of water-bath heating of normal (a) and tumour (b) tissues at different water temperatures: a) comparison of the calculated results using the linear (dotted line) and nonlinear (dashed line) models. $T_w = 45^{\circ}C$.

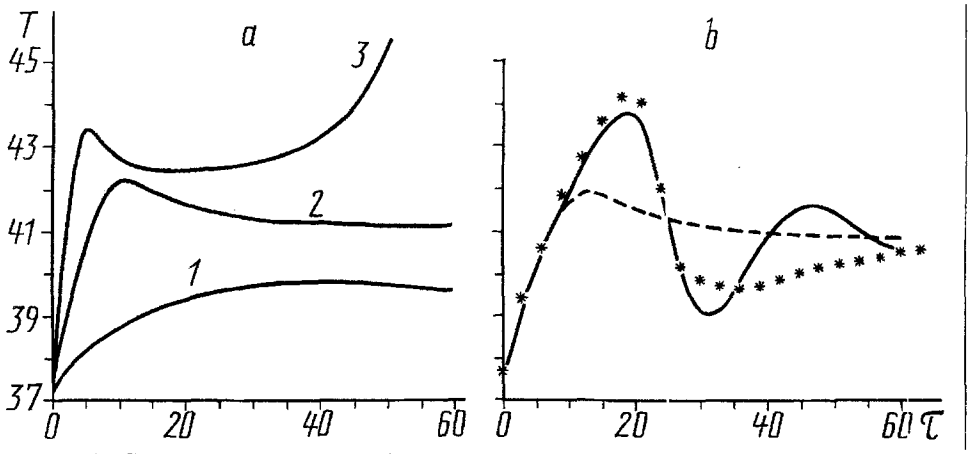

Fig. 5. SHF heating of muscle tissue at a depth of 1.5 cm: a) theoretical calculation at SAR = 20 W/kg (1), 50 (2), and 1.00 (3); b) calculation at SAR = 43 W/kg without (dashed line) and with (solid line) regard for a delay of $\tau_0 = 9$ min as compared to the data [11].

$$r\rho c \frac{\partial T}{\partial \tau} = \frac{\partial}{\partial r}\left(\lambda r \frac{\partial T}{\partial r}\right) + rQ_m + r\rho_b c_b W (T_a - T) = 0 . \qquad (9)$$

The prescribed water temperature T_w is preserved on the skin surface $r = R$. A numerical solution of (9) with regard for (5) is shown in Fig. 4a at the following parameters: $R = 0.5$ cm; $W_0 = 4.6$ mliter/(100 g·min); $\rho c = \rho_b c_b = 4$ J/(cm^3·deg); $Q_m = 0$, $\lambda = 0.38$ W/(m·°C). A similar calculation was carried out for a tumour (Eq. (9) with an account of (8), Fig. 4b). In the initial stage of heating (approximately 10 min) a monotonic temperature increase, the same for the both types of tissue, was observed, and then the temperature decreased due to perfusion enhancement.

For normal tissue, its maximum temperature was lower by approximately 1°C than the water temperature; for the tumour tissues this difference was less and approximately equal to 0.5°C. Then the temperature decreased in the normal tissue by 1–2°C, and in the tumour, by 0.5–1.0°C. Later, after 30–40 min heating the tumour temperature again began to rise and at the end of heating (60 min) was almost equal to the water temperature. As for the temperature of the muscle tissue, it remained practically unchanged and did not attain 43°C (even after of heating at $T_w = 45^{\circ}C$). These regularities of the calculated temperature curves are in fair agreement with the experimental curves [12].

Local SHF Heating by a Constant-Power Source. Despite the seeming simplicity of the problem, with such heating a number of nontrivial effects were revealed that were associated with local thermoregulation of the

organism. Thus, in [11] SHF heating of the muscle tissue of dog extremities yielded four radically different types of temperature curves:

1. A monotonic increase in tissue temperature that reached its stationary value $T \leq 41^{\circ}C$ for 10–20 min. Such a regime was observed at low values of absorbed power (SAR < 30 W/kg).

2. Having attained the maximum (5–15 min heating), the temperature decreased by 1–2°C and then remained virtually unchanged. This has been observed by many investigators [11, 19, 20]; SAR = (20–50) W/kg.

3. Periodic increases and decreases in a temperature [11]. The amplitude of the temperature fluctuations reached 7°C with a period of 20–60 min. SAR was 45–80 W/kg.

4. A temperature increase leading to irreversible changes in the tissue; SAR > 80–100 W/kg.

SHF heating of muscle tissue has been evaluated under the following assumptions: the absorbed power exponentially decreases with depth and the attenuation coefficient is 64 m^{-1}; the skin surface is air cooled at $T_a = 20^{\circ}C$ and the heat transfer coefficient $\alpha = 50$ W/($m^2 \cdot C$); and no radial heat spreading (one-dimensional heat transfer) occurs. Figure 5a shows calculation results of the temperature curves at different absorbed powers. It is seen that the model qualitatively correctly describes temperature curves of types 1, 2, and 4. The substantial divergence from curves of type 3 is due to the delayed response of the blood flow, which is substantial at high rates of temperature change. This delay has been detected in a number of experimental studies (see, e.g., [21]). To describe such a response, we assume formally that the perfusion rate in a tumour is determined by the temperature factor with delay τ_0:

$$W - W_0 = f_1 [T(\tau - \tau_0)] \Phi(\xi) = W_0 \exp [0.7\Delta T(\tau - \tau_0)] \xi \exp(-\xi). \quad (10)$$

Figure 5b shows that the model fits the experimental data [11] at $\tau_0 = 9$ min. However, the correct account of this effect needs special studies and, first of all, analysis of the response of perfusion to sudden changes in temperature. As it follows from the results of [13] such a response differs qualitatively from the response of perfusion to slow heating.

Conclusions. The thermal processes in living tissue may be described using the following scheme. In the first stage, data on the changes in perfusion at different temperatures are reduced to a single curve (for each type of tissue), and then the approximating functions f_1, f_2, and φ are determined. In the second stage, the generalized dependence is used to predict temperature fields by solving the bioheat equation.

As judged from the reported results, the proposed model describes well some known empirical regularities with a comparatively slow change in tissue temperature, which is most important from the viewpoint of clinical trials. The proposed scheme seems to be quite adequate for such processes. To enjoy successful application of the model, it is necessary to pick up extensive data about the blood flow changes in different tissues of an organism. This model is undoubtedly useful for the generalized prediction of hyperthermia. But the individual concrete prediction of thermal fields within the framework of this generalized model will be, naturally, quite approximate though use of the general regularities of changes in the human blood flow will also make it possible to improve the scheme of interactive short-range forecasting.

Sudden changes in a temperature entail a qualitatively different response of the blood flow that is not described by the TTA. Such responses are probably described by kinetic equations but their investigation is beyond the scope of the present work.

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NOTATION

T, temperature, °C; τ, time; r, distance up to the axis; λ, thermal conductivity; Q_m, metabolism heat; ρ, c, density and specific heat of the tissue; ρ_b, c_b, density and specific heat of blood; W, perfusion rate; W_0, perfusion rate at normal temperature.

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