Journal of Engineering Physics and Thermophysics, Vol. 69, No. 3, 1996

HEAT TRANSFER IN REGIONAL EXTRACORPORAL PERFUSION OF LIMBS

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UDC 536.2.072:612.014.424.5

Two problems of heat transfer in regional perfusion are analyzed, viz., in heating of limbs by hot blood and in normothermal perfusion in combination with local SHF hyperthermia. The efficiency of the procedure in the latter case and its inefficiency in the former case are shown. The coefficient of heat transfer between a circulatory system and biotissue is estimated.

Introduction. Regional extracorporal perfusion (REP), which localizes the effect of antitumoral preparations, is an effective method of the therapy of tumors of limbs [1]. However, extremely high time consumption hinders its wide introduction to clinical practice. Recent successes of vascular surgery and constant improvement of apparatuses of artificial blood circulation have renewed the interest in REP.

To strengthen the effect of drugs on tumors during REP, two types of hyperthermia of limbs were employed at the Belarusian Scientific-Research Institute of Oncology and Medical Radiology, namely, hyperthermal ("hot") perfusion and local SHF hyperthermia in combination with normothermal artificial perfusion.

Clinical experiments conducted in two groups of patients showed the absence of the therapeutic result in the case of hyperthermal perfusion: the temperature in the tumor was considerably lower than required. In the second case, with local SHF hyperthermia, one succeded in attaining the necessary temperature; therapeutic results were considerable.

A theoretical analysis of heat transfer in both the methods of artificial perfusion is the main aim of the present paper.

Hyperthermal Regional Extracorporal Perfusion. From the viewpoint of the theory of heat transfer the role of blood flow here is opposite to that observed in traditional microwave hyperthermia: in SHF heating enhancement of the blood flow hinders heating, whereas in the present case it facilitates the increase in temperature. While heating tissue, arterial blood cools more intensely in arterioles, and in capillaries it attains the temperature of the given section of the body. Therefore, the temperature of the venous main line is similar to the case of microwave hyperthermia in that it is some mean temperature of a perfused organ.

Figure 1 shows averaged curves of heating of different types of biotissues and of arterial and venous blood in clinical hyperthermal perfusion of limbs of 14 patients. Temperature of arterial blood was maintained at the level of 42°C for an hour. The fact that a tumor's temperature over the whole hour turns out to be lower than in other types of biotissue caught our attention.

A thermal model of the process of hyperthermal perfusion can be constructed on the basis of a biothermal equation

$$\rho c \frac{\partial T}{\partial \tau} = \nabla (\lambda \nabla T) - W \rho_b c_b (T - T_a) + Q_m . \qquad (1)$$

Academic Scientific Complex "A. V. Luikov Heat and Mass Transfer Institute, Academy of Sciences of Belarus," Minsk; Scientific Research Institute of Oncology and Medical Radiology, Ministry of Public Health of Belarus", Minsk, Belarus. Translated from Inzhenerno-Fizicheskii Zhurnal, Vol. 69, No. 3, pp. 434-442, May-June, 1996. Original article submitted March 20, 1996.

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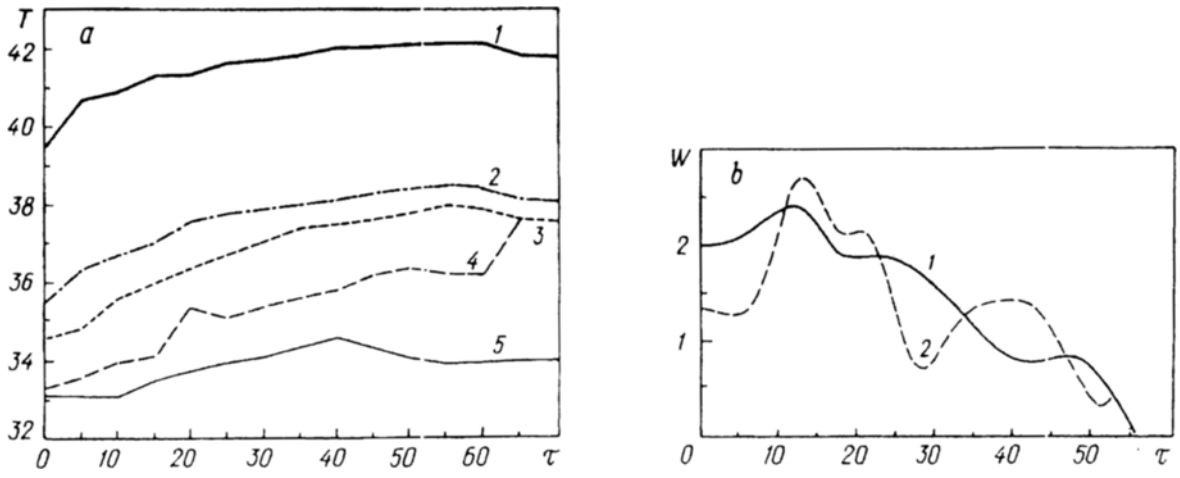

Fig. 1. Curves of heating of different biotissues in hyperthermal regional perfusion of limbs (averaged data in 14 patients: 1) arterial blood; 2) venous main line; 3) muscle below the tumor; 4) tumor; 5) hypodermal cellular tissues) (a) and perfusion in muscle (1) and tumor (2) calculated by these data and formula (8) (b). T, °C; τ, min; W, ml/100 g of biotissue.

For simplicity we use the model of a limb in the form of a cylinder where radial heat transfer is determined by the equation

$$\rho c r \frac{\partial T}{\partial \tau} = \frac{\partial}{\partial r}\left(\lambda r \frac{\partial T}{\partial r}\right) - W \rho_b c_b r (T - T_a) + r Q_m , \tag{2}$$

where r is the distance to the cylinder axis. The symmetry condition and convective heat transfer on the skin surface $r = R$ are the boundary conditions:

$$\frac{\partial T}{\partial r} = 0 \quad \text{at} \quad r = 0 , \tag{3a}$$

$$\lambda \frac{\partial T}{\partial r} = \alpha (T_c - T) \quad \text{at} \quad r = R . \tag{3b}$$

As an initial condition we use a simplified condition of homeostasis:

$$T = 37^{\circ}\text{C} \quad \text{at} \quad \tau = 0 . \tag{4}$$

We also ignore metabolism. As the results of the analysis indicate, this disregard is not always justified and then the model can be modified with allowance for this factor.

It is more difficult to take into account the kinetics of blood flow during heating. The model, developed in [2] and based on the principle of *temperature-time superposition*, was successfully used to describe local heating of biotissues. However, for the case of artificial perfusion this model requires refinement. There is probably, no need to speak of a substantial change in a total blood flow of a limb that is controlled by the apparatus of artificial blood circulation. Is the blood flow redistribution between separate parts of biotissues during heating possible? The answer to this question needs special experiments to be conducted. In this analysis two extreme versions were used:

a) blood flow redistribution does not take place; perfusion remains the same as with homeostasis during the whole process;

b) thermal regulation is fully realized and blood flow distribution obeys the same laws as in natural perfusion, i.e., it is governed by the relations given in [2]; limb perfusion in this case remains constant.

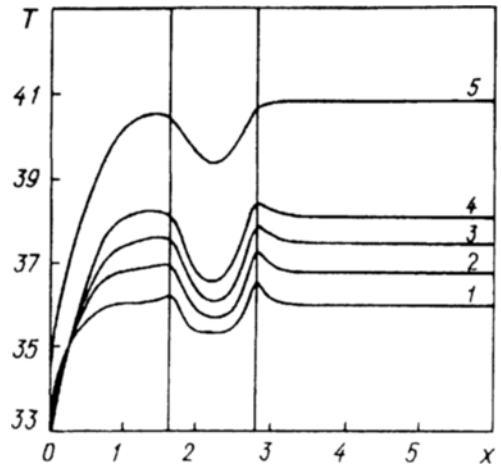

Fig. 2. Temperature profiles in hyperthermal perfusion of limbs (temperature of arterial blood 42°C): 1) after 5-min heating; 2) 10; 3) 15; 4) 20; 5) 60. x, cm.

As in [3], the model geometry included seven layers. The dimensions of layers and their thermophysical characteristics are given in Table 1 [3].

The dynamics of the change in temperature profiles is shown in Fig. 2. Gaps corresponding to the central part of the tumor are typical for them. Relatively low temperatures in the tumor remain during 60 min of heating; at the temperature of 42°C of arterial blood the temperature in the tumor does not exceed 39°C, and at T_a = 43°C it is only 40°C, that is, much smaller than required therapeutic temperatures. The temperature of the muscle tissue surrounding the tumor is 1–1.5°C higher and in the latter case amounts to about 42°C after 60 min of heating; this is close to an ultimately admissible value. This difference in temperatures of normal and tumoral tissues is caused by different perfusion of them. A weak perfusivity of the central part of the tumor does not make it possible to heat up the tumor to the needed therapeutic temperatures by forced blood circulation. This effect is exactly opposite to the effect in SHF heating where weak perfusion in the tumor allows one to heat it up to a temperature that is higher than that of surrounding tissues and achieve the necessary therapeutic result [2].

Figure 3 shows the curves of heating of different biotissues in hyperthermal perfusion. Muscles are heated more quickly due to their high perfusion; skin, which is close to the outer surface, and weakly perfused adipose tissue and the tumor are heated more slowly. The reduction of temperature in a skin layer at the initial stage of heating is caused by the adopted condition of homeostasis: actually, in normothermia the skin temperature is much smaller than 37°C and is 30–34°C.

It is of interest to compare the results of calculations in perfusion that is constant in time (Fig. 3a) and in that varying according to the model of temperature-time superposition (Fig. 3b). The general character of heating remainded unchangeable; however, in the latter case it is more intense. The comparison with the observation data (see Fig. 1) shows a better agreement between the model of constant perfusion and the test data. It is probable that in artificial perfusion the processes of thermal regulation are damped down to a great extent.

Now we consider the efficiency of heat transfer in hyperthermal REP.

Earlier it was assumed that heated blood transfers heat to tissues completely. At the same time the validity of this assumption is not obvious. Efficiency of heat exchange between a tissue and blood is determined by a number of factors: thermophysical parameters of blood, of vessel walls and surrounding biotissues, the length and diameter of a vessel, and also the blood flow rate. A theoretical analysis allows one to determine these characteristics only at the level of preliminary estimates due to the variety and complexity of the vascular structure of biotissue. Therefore, calculations of this efficiency, performed directly on the basis of experimental data, are of great interest. In [4] efficiency of heat transfer was calculated by the technique of thermal wash-out simultaneously with the calculation of the effective blood flow. Both these quantities were found from the same curve of biotissue cooling

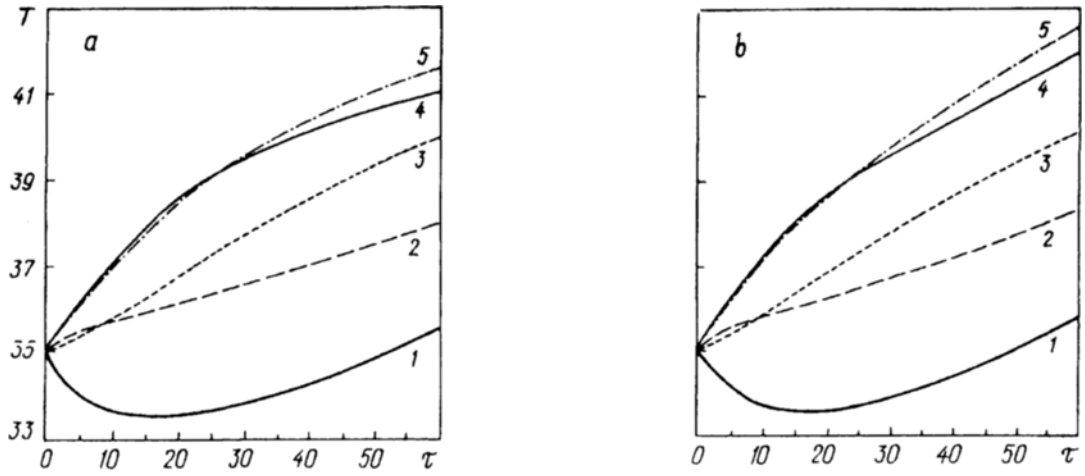

Fig. 3. Theoretical curves of heating different biotissues in hyperthermal perfusion of limbs (a) perfusion is assumed constant in each biotissue, b) perfusion changes according to temperature-time superposition): 1) skin; 2) adipose tissue; 3) tumor; 4) muscle above the tumor; 5) muscle below the tumor. Temperature of heated blood 42°C.

which probably was the reason for unsatisfactory results of the efficiency estimation (in some cases efficiency was higher than unity).

Extracorporal hyperthermal perfursion gives a good opportunity to estimate heat exchange between the circulation system and biotissues. From the viewpoint of heat transfer this heating is more convenient for analysis than CHF heating or heating in a hot water bath.

We refer to Fig. 1a again. The temperature of the venous main line always turns to be somewhat lower than for all types of biotissues. This results from incomplete heat transfer by hot blood to biotissues (in the case of 100% efficiency the temperature of the venous main line should be some mean from the temperature of biotissues). Actually, heat transfer by blood in the biothermal equation (1) should in the general case be

$$Q_b = W\rho_b c_b (T_a - T_v), \tag{5}$$

where T_v is the temperature of venous blood issuing from the given volume. Comparing (5) with the traditional form (1) we obtain that in the case of nonideal heat transfer it is necessary to introduce the coefficient of efficiency to (1)

$$\eta = \frac{T_a - T}{T_a - T_v}. \tag{6}$$

To calculate (6) it is necessary to know temperatures of coming T_a and issuing T_v blood for each portion of biotissue. A large part of the perfused biotissue of limbs consists of a muscle tissue, and therefore the mean coefficient of heat transfer efficiency can be found as

$$\eta_s = \frac{T_a - T_m}{T_a - T_v}. \tag{7}$$

Figure 4 presents the results of the efficiency calculation by Eq. (7). It appears practically constant during the whole process of heating and amounts to 0.8–0.87, thus indicating the objective character of the analysis. This coefficient of efficiency can be used to make other estimates, e.g., to determine the blood flow rate.

Neglecting the effects of heat conduction and metabolism in the biothermal equation (1), we obtain with allowance for (5)

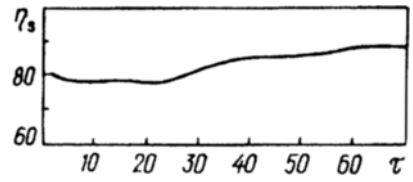

Fig. 4. Dependence of the efficiency of heat transfer between heated blood and biotissue (7).

$$W = \frac{\rho c \frac{dT}{d\tau}}{\eta \rho_b c_b (T_a - T)}. \tag{8}$$

Expression (8) makes it possible to find blood flow rate in various biotissues with the assumption of equal efficiencies of heat transfer. Figure 1b shows the results of these calculations for a muscular tissue and the tumor. The values of perfusion in both types of the tissue turned out to be very low, thus confirming the assumption of the inadequacy of the model of temperature-time superposition, based on the data of natural blood circulation, to extracorporal perfusion. An interesting specific feature of the curves in Fig. 1b is a well expressed drop of perfusion during the procedure, probably as a result of the effect of the apparatus of artificial blood circulation on blood (the change in the rigidness of erythrocytes and, as a result, blood viscosity).

The main conclusion is the following: hyperthermal perfusion does not allow tumor heating to the required therapeutic temperatures; the temperature in the tumor is lower than in normal tissues by $1-1.5^{\circ}$C and remains lower than the temperature of arterial blood by 3°C even after 60 min of heating.

Local SHF Hyperthermia of Limbs in Combination with Normothermal Perfusion. On the basis of the analysis of hyperthermal REP previsions section made a conclusion about the impossibility of attaining the necessary therapeutic temperatures and achieving a medicinal effect. How efficient can the combination of artificial perfusion of limbs with SHF heating be? Can this way be more efficient than traditional SHF heating? The answers to a great extent depend on the kinetics of the blood flow in the heated biotissue. In artificial perfusion, as shown above, the blood flow rate obeys its own special rules, which differ from those for normal blood circulation; therefore, test and clinical studies acquire a determining character.

Normothermal perfusion of limbs in combination with SHF hyperthermia (2450 MHz) was performed in 14 patients. A histological investigation done after the procedure showed that in 43% of cases tumor cells were not found, and in 21% of cases vast necrosis fields or dystrophic changes were found. These results were obtained at the temperature of 43°C and higher, i.e., a therapeutic effect was achieved mainly due to hyperthermia.

In Figs. 5a and 5b averaged curves of heating of different biotissues and mean data on the change in the power of the emitter during heating are presented. The temperature of venous and arterial blood varied slightly during heating. Probably due to the localization of radiation in the near-tumor region, a great portion of the limb was not subject to heating.

We estimate the efficiency of therapy using the concept of a thermal dose, i.e., the equivalent time of heating τ_{eq}, used in [5]

$$\tau_{eq} = \int_0^{\tau} F(T)\, dl, \tag{9}$$

where

$$\begin{aligned} F(T) &= 0, && T < 40^{\circ}\text{C}, \\ &= 4^{(T-42.5)}, && 40 < T < 42.5, \\ &= 1, && T = 42.5, \\ &= 2^{(T-42.5)}, && 42.5 < T \leq 45.5, \\ &= 8, && T > 45.5. \end{aligned} \tag{10}$$

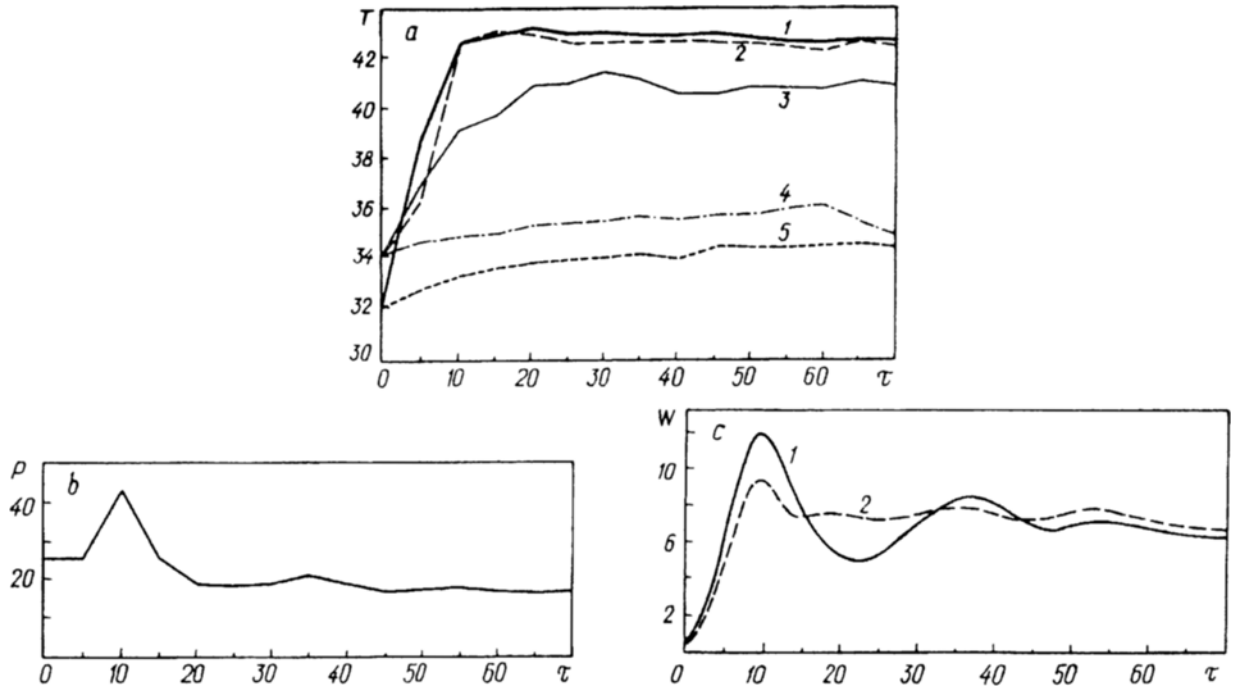

Fig. 5. Averaged curves of heating different biotissues in SHF hyperthermia of tumor by the 2450 MHz source using normothermal perfusion (1) tumor; 2) hypodermal cellular tissue above the tumor; 3) muscle below the tumor; 4) muscle beyond the radiation zone; 5) arterial blood) (a), change of mean power of a SHF emitter (b), and perfusion in the muscle (1) and tumor (2) calculated by these data and formulas (11) and (12) (c). ρ, kg/m^3.

Thermal doses in the tumor, in the hypodermic tissue above the tumor and in the muscle below the tumor were estimated by Eqs. (9) and (10). The thermal dose in a muscular tissue (75 min) was much lower than in the tumor (7 min), whereas in subcutaneous fat it increased (86 min). Consequently, in heating by the source of 2450 MHz superheating of the subcutaneous fat constituted the main hazard.

Now we evaluate how perfusion in the tumor and muscular tissue changed during heating. With heat of metabolism and heat conduction being neglected, the one-dimensional biothermal equation can be written in the form

$$W = \frac{\rho c \dfrac{dT}{d\tau} - \rho \, \mathrm{SAR}}{\rho_b c_b (T_a - T)} . \tag{11}$$

Specific SAR absorption is proportional to the decreasing power P. The value of SAR at $\tau = 0$ is found by the initial slope of the temperature curve

$$\mathrm{SAR}(\tau) = \mathrm{SAR}(0) \, P(\tau)/P(0) , \quad \mathrm{SAR}(0) = \frac{1}{c} \left. \frac{dT}{d\tau} \right|_{\tau=0} . \tag{12}$$

In Fig. 5c the curves of the change in the blood flow rate (reduced to the value ml/100 g/min) calculated by the formulas (11) and (12) are given. Perfusion both in a normal tissue and the tumor turned out to be substantially higher than normothermal values (2–5 ml/100 g/min). In muscle tissues perfusion increased during the first 10 min of heating, having achieved the maximum of 15 ml/100g/min by approximately 15 min of heating. Then it decreased rather sharply to 10 ml/100 g/min. After this reduction the blood flow in the muscle tissue again increased, though not so greatly, and varied with a damping amplitude of about 12 ml/100 g/min. In the tumor perfusion was lower than in a

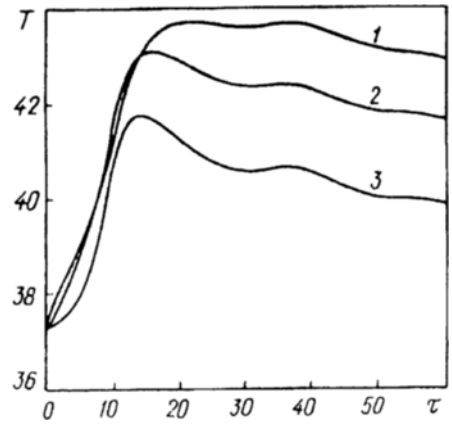

Fig. 6. Theoretical curves of heating different biotissues in normothermal perfusion in combination with local SHF hyperthermia of limbs: 1) tumor; 2) subcutaneous fat; 3) muscle.

normal tissue (maximum 13 ml/100 g/min), although the temperature in it was higher by 1–2°C. This character of perfusion variation corresponds to the known empirical laws [6]; this prompts one to use the model of local hyperthermia in which the description of the blood flow is based on the principle of temperature-time superposition [2] and is expressed by the following relations:

$$W = W_0 \left\{1 + \exp\left[\eta\,(T - 37)\right] \xi \exp\left(-\xi\right)\right\}, \tag{13}$$

$$\xi = \int_0^{\tau} a_T dt, \tag{14}$$

$$a_T = (1/\tau_0) \cdot 2^{(T - 43)}. \tag{15}$$

In [2] the following parameters were used: $\tau = 30$ min, $\eta = 0.45$ for a normal tissue, $\eta = 0.15$ for the tumor, which are estimated from the data of heating limbs of rats in a hot water bath. The character of blood flow variation (Fig. 5c) shows that in our case these parameters should be verified. Figure 6 presents the results of the calculation of local hyperthermia by the model of [2] at $\tau_0 = 60$ min. A general character and qualitative values of the temperature curves correspond to the data of Fig. 6. However, there are certain differences. A drop is observed for the computational temperature curves after reaching a maximum that is especially expressed for normal tissues, though it is absent for experimental curves. This difference is probably associated with the specific features of extracorporal blood circulation in which perfusion decreases due to the changes in blood viscosity not included in the model (see above).

In general, a combined method of SHF heating and normothermal perfusion gives positive results: one succeds in attaining necessary therapeutic temperatures in the tumor and medicinal effect.

The authors are thankful to the Fundamental Research Fund of Belarus for financing the works.

NOTATION

ρ, c, density and specific heat capacity of biotissue; ρ_b, c_b, same for blood; λ, thermal conductivity; T, temperature; T_a, T_v, T_m, T_c, temperatures of arterial blood, venous main line, muscular tissue, and surrounding medium, respectively; W, efficiency of perfusion; Q_m, heat of metabolism; α, coefficient of heat transfer on the surface; τ, time; x, distance from the skin surface.

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