

Measurement of local tissue perfusion through a minimally invasive heating bead

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Abstract A minimally invasive approach was proposed to measure local blood perfusion rate in living tissues, based on the well-known Pennes bioheat equation. The measuring probe consists of a heater covered with conductive epoxy and temperature sensor deposited on the probe–tissue interface. By monitoring the probe–tissue interface’s temperature response before and after employing the constant heat flux, the tissue blood perfusion rate can be obtained. A theoretical model was developed to describe the measurement system. In vivo experiments were performed on the rabbit’s thighs to validate this method. At last, uncertainties implied in the temperature measurement and voltage across the heater was evaluated. The results point out the way to improve the accuracy of the present method and its appropriate application occasion.

Keywords Local blood perfusion · Penne’s equation · Constant heat flux · Minimally invasive · In vivo measurement · Bioheat transfer

List of symbols

C Specific heat of tissue (J/kg K)
 C_b Specific heat of blood (J/kg K)
 K Thermal conductivity of tissue (W/m K)

Q_m Metabolic rate of tissue (W/m³)
 q_0 Heat flux passing from the bead to the tissue (W/m²)
 R Resistance of the heating wires embedded in the bead (Ω)
 R_0 Bead radius (m)
 T Tissue temperature ($^{\circ}\text{C}$)
 T_0 Initial tissue temperature ($^{\circ}\text{C}$)
 T_a Artery temperature ($^{\circ}\text{C}$)
 t Time (ms)
 U Voltage across the heating wires (V)
 ΔU Uncertainty of the voltage (V)
 W_b Blood perfusion rate (kg/m³ s)
 ΔW_b Uncertainty of the predicted blood perfusion (kg/m³ s)
 r Coordinate (m)

Greek letters

α Thermal diffusivity of tissue (m²/s)
 θ Temperature elevation due to external heating ($^{\circ}\text{C}$)
 θ_{R_0} Temperature elevation at the bead-tissue interface due to external heating ($^{\circ}\text{C}$)
 $\Delta\theta_{R_0}$ Uncertainty of the temperature ($^{\circ}\text{C}$)
 ρ Density of tissue (kg/m³)
 ρ_b Density of blood (kg/m³)

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1 Introduction

As a fundamental physiological entity, tissue blood flow in micro-circulation including the capillary net-

work plus small arterioles and venules, is usually referred to as perfusion defined as the blood flow rate per unit tissue volume. This value is of importance in cardiovascular, thermoregulatory and medical fields for practice and research. Knowledge of perfusion is becoming increasingly important for diagnostic and therapeutic medicine as well as understanding of general physiology. There is a strong need for measuring the local perfusion in small volumes of target tissue. Measurements of tissue blood flow are of great importance for development of medical science, biomedical engineering and the technology for disease diagnostics, drug studies, and cancer treatment [17].

Techniques to estimate the perfusion rate generally include non-invasive and invasive ones. Non-invasive measurements have been attempted for a long period of time and several effective approaches have been reported [1, 6, 9, 11, 18, 19, 24]. Such approaches successfully avoid causing discomfort, trauma, and possible local infections for tissue. However, the measurements were performed through skin surface. Hitherto insufficient measurement depth and poor time- or space-resolution was often encountered. A minimally invasive measurement might be one possible solution to resolve this problem. Presently available assessments of perfusion typically involve the addition of a foreign substance (dyes, radioactivity, particles) or excitation (ultrasound, X-rays, electricity, heat) into the biologic system. Localized heating has the advantage of producing no systemic effects, easy to be tolerated by biological body, and quick to dissipate heat in the surrounding tissue [26]. Therefore method has been tried by many investigators to measure perfusion. Chato's self-heated thermistor method [7] was among the first to be based on calculating the perfusion from the amount of power necessary to cause a set increase in thermistor temperature. Balasubramaniam and Bowman [5] contributed to this method by considering a more realistic sphere of thermistor. Chen and Holmes [8] postulated their thermal pulse decay (TPD) technique for simultaneous determination of local blood perfusion and tissue thermal conductivity, which has been subsequently enhanced by Arkin et al. [3, 4]. Parker [21] suggested using the same technique but proposed heating the tissue surrounding a thermocouple using a focused ultrasound transducer. The measurement error of the TPD technique becomes significant in the region where perfusion is low. Johnson et al. [12] developed a spherical probe, which is operated in a constant power mode. Patera et al. [22] changed the spherical probe to cylindrical one. Valvano and his colleague [2, 25, 26, 27] improved the thermal diffusion probe technique developed by

Bowman and his colleagues, an approach using a spherical thermistor probe operated at constant temperature. But this method requires calibration on the thermistor probes and the plot of perfusion versus the difference between the effective and intrinsic conductivities. Kress and Roemer [14] have compared a variety of perfusion estimation techniques and found that none of the transient techniques appears to be clearly superior to the others.

Clearly, each of these techniques is based on thermal phenomena and very complicated. The goal of this study is to develop a simple method for blood perfusion measurement. The probe consists of a heater covered with conductive epoxy and temperature sensor deposited on the probe-tissue interface. Power is supplied through a small thermistor bead, which was inserted in advance into the tissue. The supplied power elevates the temperature of the surrounding local tissue, which reaches the thermal equilibrium state soon. By monitoring the probe-tissue interface's temperature response before and after employing the constant heat flux, the tissue's blood perfusion rate was thus obtained. The theoretical basis for this model will be described in the paper. A series of in vivo experiments are further performed on the rabbit's thighs to validate this method. At last, uncertainties caused by the temperature elevation and voltage across the heater was studied. The present method is expected to be useful in a series of clinics and research.

2 Theoretical model

The model for this method is based upon the well known "bioheat-transfer" equation which was first expressed by Pennes [23]. This formulation is simply an energy balance between the heat conduction through the cellular portion of the tissue, the heat convection by the flow of blood in the vascular network, and the heat of metabolism. The thermoregulation mechanism of the biological bodies has been neglected because of the slight temperature increase induced. Assuming thermal equilibrium between the tissue and the venous blood, and constant isotropic tissue thermal properties, the one dimensional energy equation takes the form in spherical coordinate:

$$\frac{1}{r} \frac{\partial^2 (rT)}{\partial r^2} + W_b C_b (T_a - T)/K + \frac{Q_m(t)}{K} = \frac{1}{\alpha} \frac{\partial T}{\partial t} \quad (1)$$

where, ρ , C , K are respectively the density, specific heat and thermal conductivity of the tissue; $\alpha = K/\rho C$ is the diffusivity of tissue; C_b denotes specific heat of

blood; W_b the blood perfusion; T_a the supplying arterial blood temperature which is treated as a constant, and T the tissue temperature, Q_m is the metabolic volumetric heat generation rate.

The heating strategy to measure the blood perfusion is shown in Fig. 1. At the tissue-bead interface, the heat flux is considered as the constant. At the distant site far from the bead, this constant heating almost has no influence on the temperature there. The boundary and initial conditions to Eq. (1) can then be expressed as:

$$-K \cdot \frac{\partial T}{\partial r} \Big|_{r=R_0} = q_0, \quad r = R_0 \tag{2a}$$

$$\frac{\partial T}{\partial r} = 0, \quad r = \infty \tag{2b}$$

$$T(r, 0) = T_0(r), \quad t = 0 \tag{2c}$$

where, $T_0(r)$ is the initial temperature of the tissue before inserting the probe into the tissue, R_0 is the bead radius, q_0 is the heat flux passing from the bead to the tissue. In this study, the electrical current for the heater is supplied by the DC power. The heat flux could then be obtained as:

$$q_0 = U^2 / 4\pi R R_0^2 \tag{3}$$

where, U is the voltage applied on the heater, $R = 36 \Omega$ is the electrical resistance of the heater in the heated probe under room temperature (25°C). The heater is made of constantan whose main feature is its resistance which is constant over a wide range of temperatures [31].

To calculate the transient tissue temperature field due to varied environment, the steady state temperature distribution $T_0(r)$ needs to be known. It repre-

sents the basal state of living tissues, and can be obtained through solving the following equation:

$$\frac{1}{r} \frac{\partial^2(rT_0)}{\partial r^2} + W_b C_b (T_a - T_0) / K + \frac{Q_{m0}}{K} = 0 \tag{4}$$

The temperature increments used during the experiment are very low in our study. Then we assumed that the metabolic heat $Q_m(t)$ is similar to that in the steady state Q_{m0} . Subtracting the steady-state temperature field from Eq. (1), one has

$$\frac{1}{r} \frac{\partial^2(r\theta)}{\partial r^2} - W_b C_b \theta / K = \frac{1}{\alpha} \frac{\partial \theta}{\partial t} \tag{5}$$

where $\theta(r, t) = T(r, t) - T_0(r)$ is the tissue temperature elevation due to the constant heating by the bead.

The boundary and initial conditions Eq. (2) then has the form:

$$-K \cdot \frac{\partial \theta}{\partial r} \Big|_{r=R_0} = q_0, \quad r = R_0 \tag{5a}$$

$$\frac{\partial \theta}{\partial r} = 0, \quad r = \infty \tag{5b}$$

$$\theta(r, 0) = 0, \quad t = 0 \tag{5c}$$

In the present method, two steps are involved to impose the constant heat flux at the bead-tissue surface ($r = R_0$). The first is to insert the bead to the small selected volume of a target tissue. The bead is so small that it reaches thermal equilibrium with the surrounding tissue within a short time. Then, the power is switched on, until the temperature elevation at the bead reaches its steady state. Through solving Eq. (5) at the time of $t \rightarrow \infty$, the final elevated tissue temperature could be obtained as:

$$\theta(r, t \rightarrow \infty) = \frac{1}{r} \left[\frac{q_0 R_0 \exp(-\sqrt{D}r)}{K(1/R_0 + \sqrt{D}) \exp(-\sqrt{D}R_0)} \right] \tag{6}$$

where, $D = W_b C_b / K$. The temperature $\theta(r = R_0, t \rightarrow \infty) = \theta_{R_0}$ at the bead-tissue interface then reads as:

$$\theta_{R_0} = \frac{q_0}{K(1/R_0 + \sqrt{D})} \tag{7}$$

Substituting $D = W_b C_b / K$ into Eq. (7), one has

$$W_b = \left(\frac{q_0}{K\theta_{R_0}} - \frac{1}{R_0} \right)^2 \cdot \frac{K}{C_b} \tag{8}$$

Then, the blood perfusion W_b can be expressed as

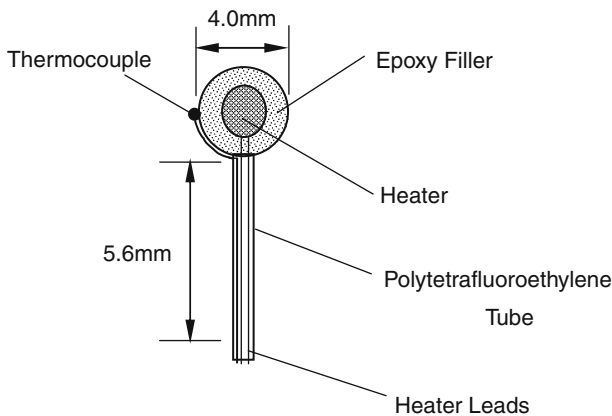


Fig. 1 Cross section of the probe

$$W_b = \left(\frac{U^2}{4\pi K \theta_{R_0} R R_0^2} - \frac{1}{R_0} \right)^2 \cdot \frac{K}{C_b} \quad (9)$$

Generally, typical values for the tissue properties are approximately constant and used as: $C = C_b = 4,200 \text{ J/kg } ^\circ\text{C}$, $K = 0.5 \text{ W/m } ^\circ\text{C}$ [10]. From this equation, if the voltage across the heater U is specified, then the blood perfusion W_b can be estimated by simply measuring the bead-tissue surface temperature elevation θ_{R_0} .

3 Experimental methods

In practice, a heating element is needed to deliver heat to the local tissue and then elevate its temperature. Additionally, a temperature sensing device is needed to measure the deviation of the temperature from steady state. These two devices should be placed at the same point to create a constant heat flux/temperature measuring device (HFTD), so that the conditions will be comparable to the situation depicted by the theoretical model. Additionally, the size of the bead should be small enough to comply with the boundary condition [Eq. (2b)]. With this guidance the manufacture of the HFTD and the measurement system will be given in this section.

3.1 The heated thermocouple probe

The heating device, shown in Figs. 1 and 2, is spherical to reduce the analytical model to one-dimension. The small heater is fabricated by winding 0.1 mm-dia constantan wire around a 2 mm-dia polytetrafluoroethylene tube. The space around the heater is filled with conductive epoxy (whose thermal conductivity is 0.503 W/m K [12]) to enhance efficient heat transfer to the surrounding tissue. The epoxy coating the entire



Fig. 2 Closeup of probe

assembly's surface is electrically insulated from the surrounding medium. The bead diameter is kept small to avoid unnecessary trauma during its inserting into living tissue. In this study, diameter of the probe was designed as 4.0 mm and the resistance of the heated probe is measured as 36Ω . The probe's copper-constantan thermocouple is placed on the sphere's equator as shown in Fig. 1. The polytetrafluoroethylene tube has a small hole through which the 0.1 mm-dia heater leads are pulled out.

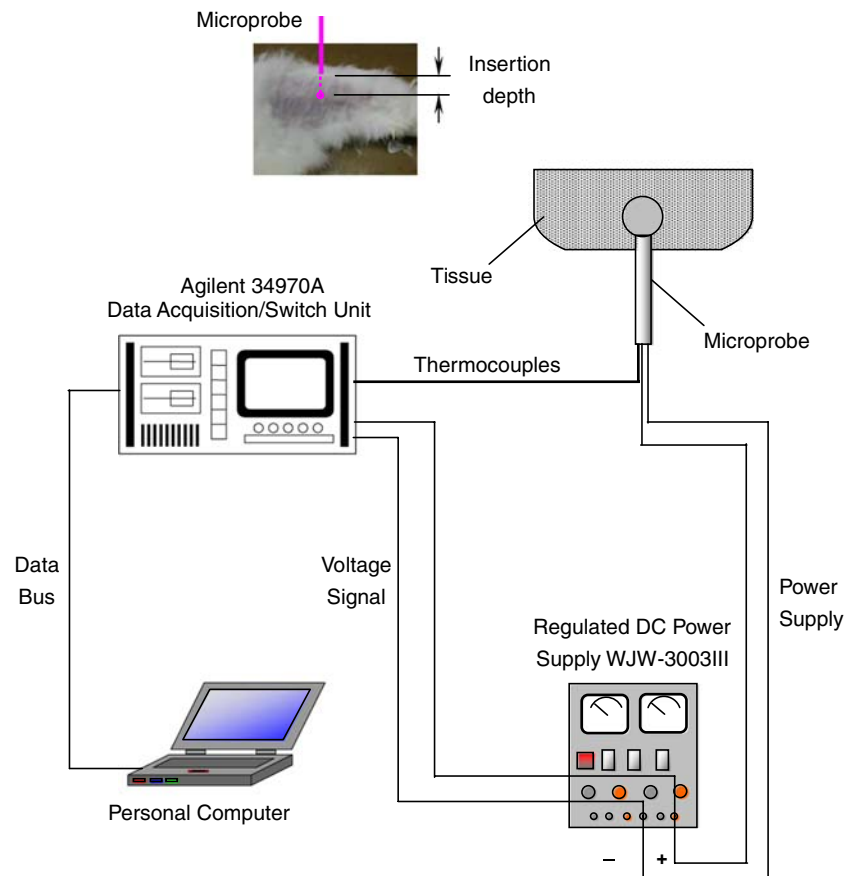
3.2 Local blood perfusion measurement system

In this study, new apparatus and experimental procedure have been developed to facilitate a systematic study of local blood perfusion. The schematic diagram of the apparatus is given in Fig. 3. The electrical current for the heater is controlled by Regulated DC Power Supply WJW-3003III, whose working voltage range is 0–5 V. The thermocouples are calibrated in the ice water and an accuracy of $\pm 0.1^\circ\text{C}$ is obtained. The bead-tissue interface transient temperature and voltage across the heater are obtained using a 48 channels HP Agilent 34970 Data Acquisition/Switch Unit. The HP Agilent 34970 Data Acquisition/Switch Unit is connected with the personal computer with the data acquisition card (HP E2078, USA). The acquisition software uses HP BenchLink Data Logger, which can immediately display, analyze and save the input measurement data.

3.3 Preparation for the in-vivo studies

During the in vivo experiments, a healthy, female rabbit with a body weight of 2.2 kg was used in this experiment. Study was performed on the muscle tissue of rabbit thighs to measure the local blood perfusion constant heat flux. The rabbit was intubated after anesthesia induced by intravenous infusion of urethane (25%, 4 ml/kg). After allowing a period of 10 min for the anesthetic to become fully effective, a 4 mm-dia medicinal needle was inserted into the rabbit thigh and drew out quickly. Then the bead was subsequently inserted into the tissue following the same path. This made the bead capable of piercing the tissue with minimal resistance. During the course of experiments, an attempt was made to keep the rabbit's level of anesthesia as low as possible. Additional anesthetic was not administered. The rabbit was placed on the test-bed and the probe and thermocouple were inserted into the specified sites. The other thermocouple was placed on the rabbit armpit to monitor the physiological conditions. The voltage was changed after the temperature reached the steady state.

Fig. 3 Schematic diagram to measure blood perfusion



In the same way three different sites were measured. All temperature and voltages sampling were carried out with a Data Acquisition/Switch Unit (Agilent 34970A, USA) and displayed at 1 s intervals by the computer.

The protocol was approved by the Animal Care Committee of Zoology Institute, Chinese Academy of Sciences. All experiments were performed according to the Guidelines for Animal Experiments, Zoology Institute, Chinese Academy of Sciences. No complications occurred in the subject examined.

4 Uncertainty analysis

In previous sections, the theoretical concept and design of the system developed were discussed. The performance of this system depends on the quality of the process to manufacture and assemble the components of the system. Any imperfection thus involved will cause measuring error, which is defined as the difference between a measured perfusion and its true value. It occurs due to various factors, which should be analysed and controlled in order to minimize the measuring error. The following section focuses on

estimating the measuring error. The uncertainty caused by thermal properties of tissue such as thermal conductivity which depends on the kinds of tissues and the individual differences will not be discussed in this study. Many methods have been used to measure the thermal conductivity of tissue in a wide temperature range [16, 29, 30]. In our study, muscle tissue of rabbit thighs was used to measure the local blood perfusion and the typical thermal conductivity of rabbit thighs was obtained from the above references.

The blood perfusion W_b can be expressed as a function of the tissue thermal, probe geometrical and electrical parameters as

$$W_b = f(U, K, C_b, \theta_{R_0}, R, R_0) \quad (10)$$

If all the exact tissue thermal, probe geometrical and electrical parameters were measured, the measured blood perfusion can reasonably be regarded as the real value. However, no measurement is perfectly accurate. Thus the blood perfusion predicted will deviate with its real value due to the uncertain parameters.

The same probe was used for all experiments. In this experiment, only the voltage across the heater U , the probe geometrical and electrical parameters R_0 , R ,

and temperature elevation θ_{R_0} must be measured. The tissue thermal properties K , C_b are generally constant due to the very low temperature increments, uncertainties caused by them will not be considered in this study.

Suppose ΔW_b is uncertainty of the predicted blood perfusion due to the approximate parameters, one can write [13, 15]:

$$\Delta W_b = \sqrt{\left(\frac{\partial W_b}{\partial U} \Delta U\right)^2 + \left(\frac{\partial W_b}{\partial \theta_{R_0}} \Delta \theta_{R_0}\right)^2 + \left(\frac{\partial W_b}{\partial R} \Delta R\right)^2 + \left(\frac{\partial W_b}{\partial R_0} \Delta R_0\right)^2} \quad (11)$$

where Δ stands for uncertainty for the corresponding variable. Equation (11) can further be expressed as follow:

$$\frac{\Delta W_b}{W_b} = \sqrt{\left(\frac{\partial \ln W_b}{\partial \ln U} \frac{\Delta U}{U}\right)^2 + \left(\frac{\partial \ln W_b}{\partial \ln \theta_{R_0}} \frac{\Delta \theta_{R_0}}{\theta_{R_0}}\right)^2 + \left(\frac{\partial \ln W_b}{\partial \ln R} \frac{\Delta R}{R}\right)^2 + \left(\frac{\partial \ln W_b}{\partial \ln R_0} \frac{\Delta R_0}{R_0}\right)^2} \quad (12)$$

The uncertainty limit of the two parameters will be studied. This result is expected to be important for estimating the accuracy of this perfusion measuring method.

5 Experimental results and discussion

5.1 Experimental results

The probe was inserted in the rabbit right thigh to evaluate the local blood perfusion at three different depths: 1.05, 1.55 and 2.35 cm (The insertion depth is the distance between the center of the probe and the up surface of rabbit thigh as shown in Fig. 3). The initial tissue temperatures at these positions are 35.4, 36.7 and 35.7°C, respectively. The initial tissue temperature at 2.35 cm is lower than that at 1.55 cm. The probe may be inserted so deep that it approaches the other surface of the rabbit thigh. Figure 4 shows the transient probe-tissue interface's temperature and voltage across the heater. The muscle temperature responded instantly as soon as the voltage across the heater changed and reached thermal equilibrium (about 250 s). Therefore, the metrical results were the local blood perfusion in steady state. As shown in Fig. 5 and Table 1, the results are similar to that of Johnson et al. [12], which was obtained with the analysis of the heated thermocouple probe's temperature transients. The local blood perfu-

sions have no obvious variations at different positions. They all express the mean blood perfusion of the rabbit thigh. It is noticed that the blood perfusion would change with the temperature [28]. Due to the small heating flux, the change could not be seen in Fig. 5 and Table 1. However, the estimated blood perfusion results appeared as a little higher than the blood perfusion in normal tissue temperature.

Table 1 gives the uncertainties caused by R_0 , R , U and θ_{R_0} with the Eq. (11). The uncertainty of the calculated blood perfusion decreased for large tempera-

ture elevation. This implies that the HFTD method has high accuracy in large temperature elevation. However, the blood perfusion would change with the strong enough heating. Therefore the appropriate temperature elevation and other parameters must be studied to improve the resolution of blood perfusion measurement with this method.

At first, the imperfection and asymmetry of the geometrical parameters of the probe will induce measurement error. The bead must be made as a sphere, which guarantees that the tissue temperature could be characterized with the one-dimensional Penne's bioheat equation in spherical coordinate system. This measurement uncertainty is caused due to fabrication and will not be discussed in this paper. The diameter is measured by screw micrometer, whose resolution is 0.01 mm. Uncertainties caused by this parameter appear so small that could be neglect in this study. The heater is made of constantan and thermal resistance coefficient is about $0.00001^\circ\text{C}^{-1}$ [31]. Thus, the effect of the temperature on the electrical resistance of the probe could be ignored. For the same reason for probe diameter, the electrical parameter R has minor effect on the measurement of the blood perfusion, when only considering the measurement resolution.

Therefore, the temperature elevation θ_{R_0} and voltage across the heater U are the most critical parameters, which are obtained using a 48 channels HP

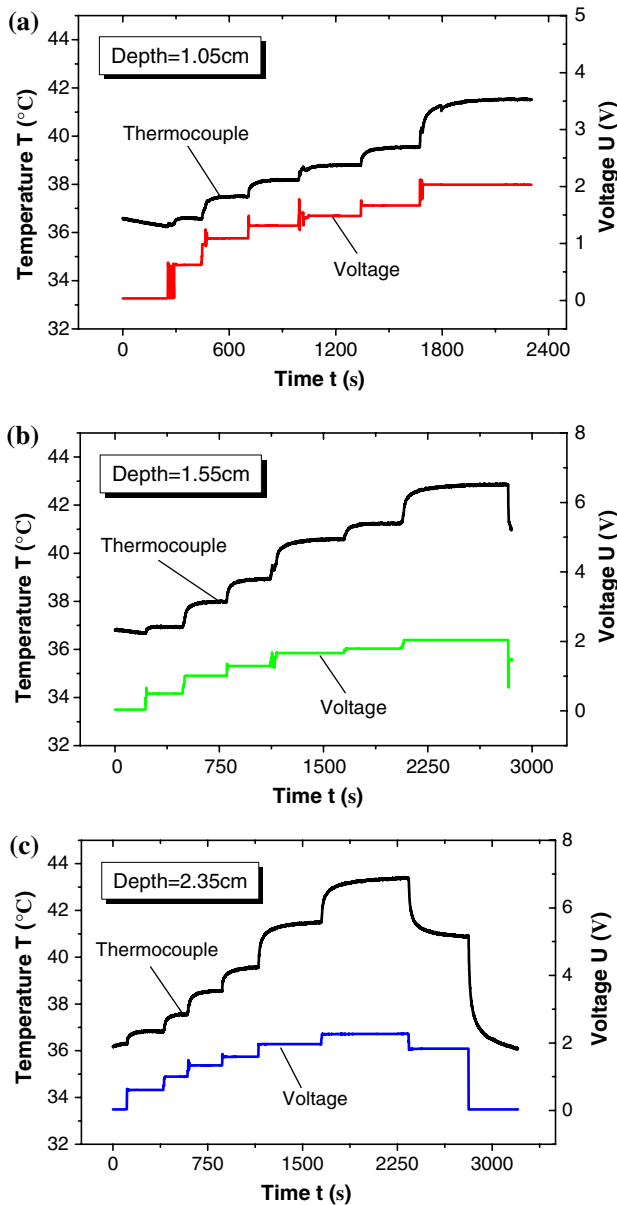


Fig. 4 Probe-tissue interface's temperature response to different voltages at three positions

Agilent 34970 Data Acquisition/Switch Unit. The measurement resolution of them are 0.1°C and 0.0001 V , respectively. The uncertainty of the calculated blood perfusion decreased for high temperature elevation (seen in Table 1). Further calculation gives that the influence of the temperature uncertainty is much greater than the voltage uncertainty. In order to improve the accuracy of the method, the thermocouple could be changed with thermistor thermometer to measure the bead-tissue interface's temperature. The uncertainty of the temperature measured by thermistor thermometer could be obtained 0.01°C , which could greatly improve the accuracy of the method. Separat-

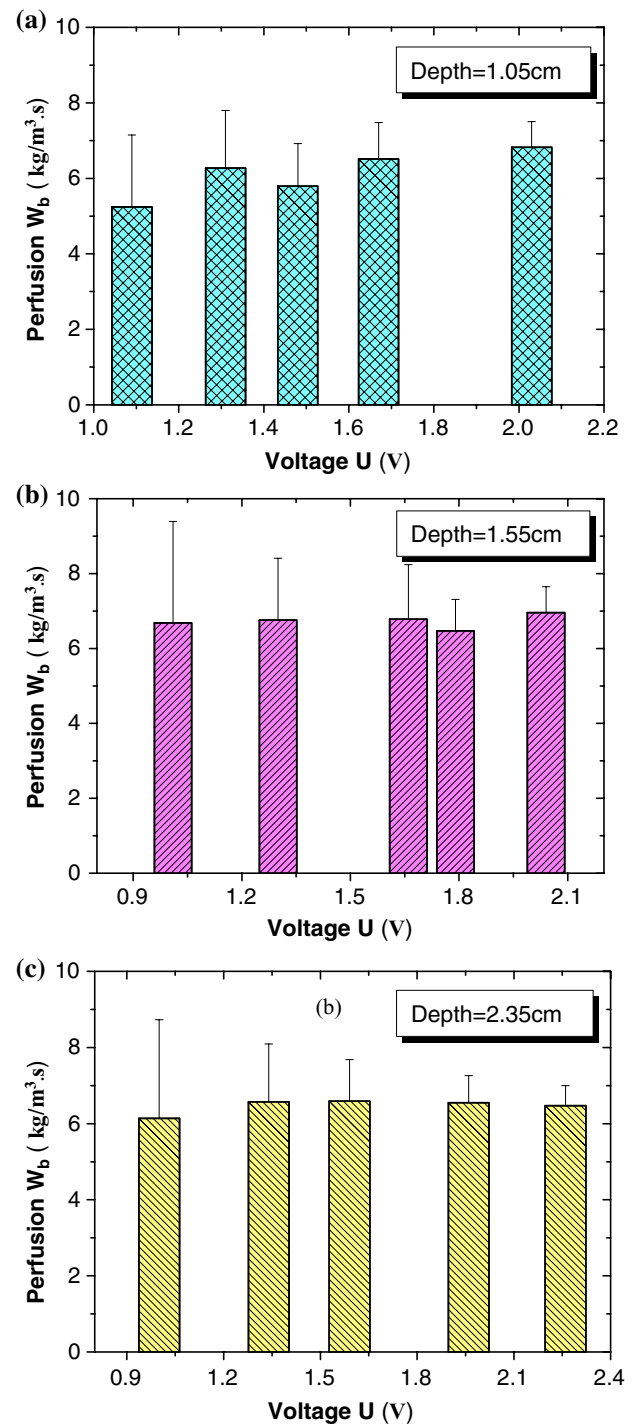


Fig. 5 Measured blood perfusion under different constant heat flux

ing the heater from the polytetrafluoroethylene (as shown in Fig. 2) is another good method to improve the accuracy of this method which could make the heat transfer in the probe more spherically symmetric. In the theoretical model, 2 cm is assumed as the distant site far from the bead. Thus, the distance between the

Table 1 Measured blood perfusion under different constant heat flux

Depth (cm)	Voltage (U), temperature elevation (θ_{R_0}) and blood perfusion (W_b)						
1.05	U (V)	0	1.09	1.31	1.48	1.67	2.03
	θ_{R_0} ($^{\circ}$ C)	0	1.85	2.60	3.36	4.20	6.16
	W_b ($\text{kg}/\text{m}^3 \text{ s}$)	/	5.24 ± 1.91	6.27 ± 1.53	5.79 ± 1.13	6.51 ± 0.97	6.82 ± 0.68
1.55	U (V)	0	1.01	1.30	1.66	1.79	2.04
	θ_{R_0} ($^{\circ}$ C)	0	1.53	2.53	3.83	4.83	6.20
	W_b ($\text{kg}/\text{m}^3 \text{ s}$)	/	6.68 ± 2.71	6.76 ± 1.65	6.78 ± 1.46	6.47 ± 0.84	6.96 ± 0.69
2.35	U (V)	0	1.0	1.34	1.59	1.96	2.26
	θ_{R_0} ($^{\circ}$ C)	0	1.52	2.70	3.80	5.78	7.70
	W_b ($\text{kg}/\text{m}^3 \text{ s}$)	/	6.14 ± 2.59	6.57 ± 1.52	6.59 ± 1.09	6.55 ± 0.71	6.47 ± 0.53

probe and each surface of tissue should be more than 2 cm in the optimal case.

The results implied that the temperature has gigantic effect on the blood perfusion measurement. In order to improve the resolution of this method, the reference temperature sensor must be in a location other than a large blood vessel. The history of the blood flow can cause fluctuations of the reference thermocouple's voltage potential when the reference thermocouple is near the vessel. The HFTD method is suitable to measure the blood perfusion far away from the large blood vessel. At the same time, large bleed must be avoided during the experiment which will influence the transfer between probe and tissue.

5.2 Validation

To verify whether the above estimated perfusion is the real value for the rabbit thigh, additional theoretical analysis was performed. Generally speaking, if the theoretically predicted temperature response using the estimated perfusion fits the experimentally measured temperature under the same conditions, then this perfusion can be regarded as the real one. In this experiment, the probe-tissue interface's temperature response has been obtained. This valuable information will be used to validate the present model. Before heating the bead, the probe was inserted into the rabbit thigh. Once their temperatures becomes identical, i.e., being in the thermal equilibrium, switch on the heating circuit with a constant voltage, then a constant heat flux will be applied to the tissue due to the small thermal resistance coefficient. The transient temperature response of living tissues subjected to the constant surface flux heating could be obtained by theoretical model (refer to Appendix). Drawing together the theoretical and experimentally results under the same condition in Fig. 6, one can find that both curves fit each other. This indicates that the measured perfusion can represent the real value for the tested rabbit thigh.

In Fig. 6, there exists a relatively large difference between the predicted and the monitored bead-tissue interface temperature at the early stage of the heating. One reason may be due to the approximation in calculation the heating power. The theoretical base of the experiment assumed that the applied heating almost has no influence on the temperature at the distant site far from the bead ($r = \infty$). In the fact, the thick of rabbit thigh is almost 3 cm. This approximation is correct when the applied heating is not too large. Another reason may be attributed to the placement of the copper-constantan thermocouple, which is buried on the bead's equator with epoxy. The thermocouple is attached to the bead tightly while the tissue is relaxed muscle when the rabbit is under anesthesia. There is a small temperature difference between the surfaces of thermocouple and tissue due to the incompact contact. When switching on the heating circuit, the bead itself will also be heated, thus, the real temperature applied on the tissue is higher than the value calculated with Eq. (A9). Therefore, the measured bead-tissue interface temperature increase appears a little higher than the theoretically predicted result. Since the theoretically predicted temperature using the above estimated perfusion fits closely the measured temperature, it provides encouraging evidence that the measurement perfusion is acceptable.

As indicated in Fig. 6, the measured temperature has some small oscillations. In order to make sure the reason, additional experiments were performed. The same copper-constantan thermocouple was inserted into the water and measured the temperature of the water (shown in Fig. 7). The temperature of water is about 26.65°C and the measured error is about 0.05°C . A section of temperature response in Fig. 6(b) approaching the thermal equilibrium is enlarged as shown in Fig. 8. The oscillation is also about 0.05°C . Comparing Fig. 8 with Fig. 7, the oscillation could be considered as the measured error and the blood perfusion almost has no influence on this oscillation.

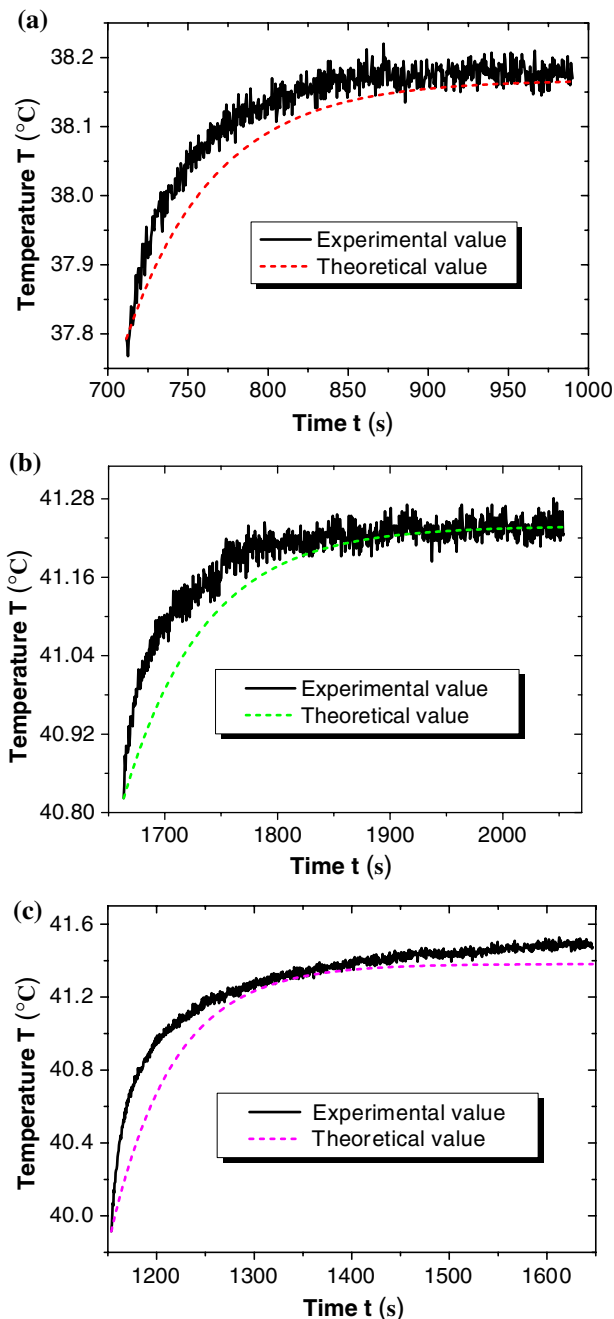


Fig. 6 Comparison between the measured surface temperature and the theoretically predicted value using the estimated blood perfusion: **a** depth = 1.05 cm, $U = 1.31$ V; **b** depth = 1.55 cm, $U = 1.79$ V; **c** depth = 2.35 cm, $U = 1.96$ V

6 Conclusions

Previous heated thermocouple probe required complicated measurement and analytical system. The present study presents a simple approach to measure local blood perfusion based on an analytical solution of the Penne's bioheat equation, for a hollow sphere heated in inner boundary by constant heating flux. This

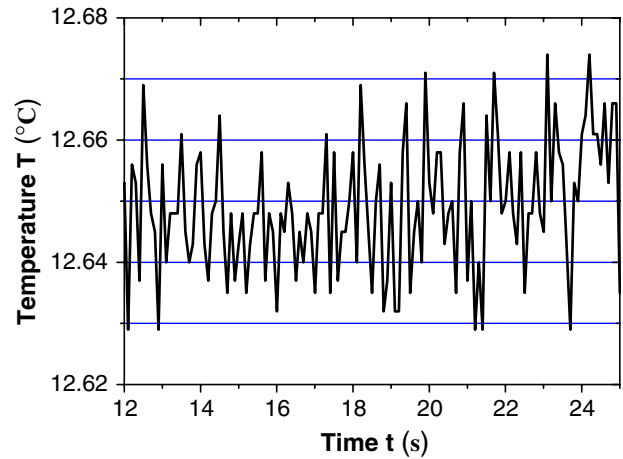


Fig. 7 The temperature of the water

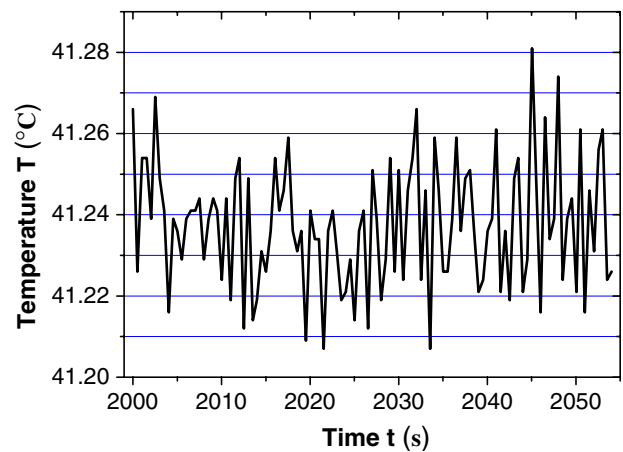


Fig. 8 A section of steady-state temperature in Fig. 6b depth = 1.55 cm, $U = 1.79$ V

method only depends on the probe–tissue interface's temperature elevation and the voltage applied on the heater. For on-line measurements, the method enables a fast and simple evaluation of tissue blood perfusion. The small size of the thermistor bead could minimize the trauma caused to the tissue, which is far below the level considered deleterious to the viability of the tissue. A preliminary probe is given in the present work, which could be made in smaller size.

A series of in vivo experiments were further performed on the rabbit's thighs. The results were similar to that of the former reports measured by other methods. In addition, uncertainties caused by the temperature elevation and voltage across the heater were studied in this paper. Further simplification on the present instrument can help to make a compact and cheap perfusion measuring device, which will have significant application in clinical practices.

Acknowledgments This work is partially supported by the National Natural Science Foundation of China.

7 Appendix: Temperature response of living tissue subjected to constant surface flux heating

To analyze the transient temperature response of living tissues subjected to the constant surface flux heating, the theoretical model was established as follows,

$$\frac{1}{r} \frac{\partial^2(rT)}{\partial r^2} + W_b C_b (T_a - T)/K + \frac{Q_m(t)}{K} = \frac{1}{\alpha} \frac{\partial T}{\partial t} \quad (\text{A1})$$

At the distant site far from the bead, the constant heating almost has no influence on the temperature there. In order to solve the question, at $r = R' = 0.02$ m is assumed as the distant site far from the bead. The equilibrium temperature under a constant voltage is the initial temperature at the following heating process. Then boundary and initial conditions to Eq. (A1) can then be expressed as:

$$-K \cdot \frac{\partial T}{\partial r} \Big|_{r=R_0} = q_0, \quad r = R_0 \quad (\text{A2a})$$

$$\frac{\partial T}{\partial r} = 0, \quad r = R' \quad (\text{A2b})$$

$$T(r, 0) = T_0, \quad t = 0 \quad (\text{A2c})$$

Assuming

$$T(r, t) = T_0 + \psi(r, t) \exp\left(-\frac{W_b C_b}{\rho C} t\right) \quad (\text{A3})$$

Then Eqs. (A1–A2a, b, c) are transformed into

$$\frac{\partial^2 \psi}{\partial r^2} + \frac{2}{r} \frac{\partial \psi}{\partial r} = \frac{1}{\alpha} \frac{\partial \psi}{\partial t} \quad (\text{A4})$$

$$-K \cdot \frac{\partial \psi}{\partial r} \Big|_{r=R_0} = q_0 \exp\left(\frac{W_b C_b}{\rho C} t\right), \quad r = R_0 \quad (\text{A5a})$$

$$\frac{\partial \psi}{\partial r} = 0, \quad r = R' \quad (\text{A5b})$$

$$\psi(r, 0) = 0, \quad t = 0 \quad (\text{A5c})$$

If the Green's function for the above Eq. (A4) is obtained, the transient tissue temperature can easily be constructed [20]. Through introducing an auxiliary problem corresponding to Eq. (A4), the Green's function can finally be obtained as (detailed derivation is omitted here)

$$G(r, t|r', \tau) = 3/(b^3 - a^3) + \frac{1}{r \cdot r'} \sum_{m=1}^{\infty} e^{-\alpha \beta_m^2 (t-\tau)} \{ \beta_m \cos [\beta_m (r - R_0)] + \sin [\beta_m (r - R_0)]/R_0 \} \times \frac{2}{(\beta_m^2 + 1/R_0^2) [(R' - R_0) - 1/[R'(\beta_m^2 + 1/R^2)]] + 1/R_0} \times \{ \beta_m \cos [\beta_m (r' - R_0)] + \sin [\beta_m (r' - R_0)]/R_0 \} \quad (\text{A6})$$

where β_m 's are the positive roots of

$$\tan \beta_m (R' - R_0) = \frac{\beta_m (1/R_0 + 1/R')}{\beta_m^2 - 1/R' R_0} \quad (\text{A7})$$

Then the tissue temperature field could be constructed with Eq. (A3)

$$T(r, t) = T_0 + \frac{3\alpha R_0^2 q_0 (1 - e^{-(W_b C_b/\rho C)t})}{K(R^3 - R_0^3)(W_b C_b/\rho C)} + \frac{\alpha R_0}{K r} \sum_{m=1}^{\infty} \frac{\beta_m}{W_b C_b/\rho C + \alpha \beta_m^2} \left(1 - e^{-(W_b C_b/\rho C + \alpha \beta_m^2)t}\right) \times \{ \beta_m \cos [\beta_m (r - R_0)] + \sin [\beta_m (r - R_0)]/R_0 \} \times \frac{2}{(\beta_m^2 + 1/R_0^2) [(R' - R_0) - 1/[R'(\beta_m^2 + 1/R^2)]] + 1/R_0} \quad (\text{A8})$$

The final solution for bead-tissue interface temperature $T(R_0, t)$ is therefore in the form of

$$T(R_0, t) = T_0 + \frac{3\alpha R_0^2 q_0 (1 - e^{-W_b C_b t/\rho C})}{K(R^3 - R_0^3)(W_b C_b/\rho C)} + \frac{\alpha}{K} \sum_{m=1}^{\infty} \frac{2\beta_m^2}{W_b C_b/\rho C + \alpha \beta_m^2} \left(1 - e^{-(W_b C_b/\rho C + \alpha \beta_m^2)t}\right) \times \frac{1}{(\beta_m^2 + 1/R_0^2) [(R' - R_0) - 1/[R'(\beta_m^2 + 1/R^2)]] + 1/R_0} \quad (\text{A9})$$

References

1. Anderson GT, Burnside G (1990) A noninvasive technique to measure perfusion using a focused ultrasound heating sources and a tissue surface temperature measurement. *Advances in measuring and computing temperatures in biomedicine: HTD-vol.147*, The winter annual meeting of ASME, Dallas, Texas, pp 31–35
2. Anderson GT, Valvano JW, Santos RR (1992) Self-heated thermistor measurements of perfusion. *IEEE Trans Biomed Eng* 39:877–885
3. Arkin H, Holmes KR, Chen MM (1986) A sensitivity analysis of the thermal pulse decay method for measurement of

- local tissue conductivity and blood perfusion. *ASME J Biomech Eng* 108:208–214
4. Arkin H, Holmes KR, Chen MM (1989) A technique for measuring the thermal conductivity and evaluating the ‘apparent conductivity’ concept in biomaterials. *ASME J Biomech Eng* 111:276–282
 5. Balasubramaniam TA, Bowman HF (1974) Temperature field due to a time dependent heat source of spherical geometry in an infinite medium. *ASME J Heat Transf* 93:296–299
 6. Castellana FS, Skalak R, Cho JM, Case RB (1983) Steady-state analysis and evaluation of a new thermal sensor for surface measurements of tissue perfusion. *Ann Biomed Eng* 11:101–115
 7. Chato JC (1968) A method for the measurement of thermal properties of biological materials. Thermal problems in biotechnology, American society of mechanical engineers, LCN068–58741, New York, pp 16–25
 8. Chen MM, Holmes KR (1984) The thermal pulse-decay method for simultaneous measurement the thermal conductivity and local blood perfusion rate of living tissues. *Advances in bioengineering*. Sponsored by: ASME, pp 113–115
 9. Fouquet Y, Hager JM, Terrell J, Diller TE (1993) Blood perfusion estimation from noninvasive heat flux measurements. In: Roemer RB (ed) *Advances in bio-heat and mass transfer: microscale analysis of thermal injury processes, instrumentation, modeling, and clinical applications*. ASME, New York, pp 53–60
 10. Holmes H R (1997) Biological structures and heat transfer report from the Allerton Workshop on the Future of Bio-thermal Engineering.
 11. Holti G, Mitchell KW (1979) Estimation of the nutrient skin blood flow using a non-invasive segmented thermal clearance probe. In: Rolfe P (ed) *Non-invasive physiological measurements*, vol 1. Academic Press, London, pp 113–123
 12. Johnson WR, Abdelmessih AH, Grayson J (1979) Blood perfusion measurements by the analysis of the heated thermocouple probe’s temperature transients. *ASME J Biomech Eng* 101:58–65
 13. Kline SJ (1985) The purpose of the uncertainty analysis. *ASME J Fluids Eng* 107:153–160
 14. Kress R, Roemer R (1987) A comparative analysis of thermal blood perfusion measurement techniques. *ASME J Biomech Eng* 109:218–225
 15. Liu J (2001) Uncertainty analysis for temperature prediction of biological bodies subject to randomly spatial heating. *J Biomech* 34:1637–1642
 16. Liu J, Wang CC (1997) *Bioheat transfer* (in Chinese). Science Press of China, Beijing
 17. Liu J, Xu LX (1999) Estimation of blood perfusion using phase shift in temperature response to the sinusoidal heating at the skin surface. *IEEE Trans Biomed Eng* 46:1037–1043
 18. Michener MD, Hager JM, Terrell JP, Veit H, Diller TE (1991) Noninvasive blood perfusion measurement with a heat flux microsensor. In: McGrath JJ (eds) *Advances in biological heat and mass transfer*. ASME, New York, pp 1–8
 19. O’Reilly TB, Gonzales TL, Diller TE (1996) Development of a non-invasive blood perfusion probe. In: Hayes LJ, Clegg S (eds) *Advances in biological heat and mass transfer*, HTD-vol.337/BED, vol 34. ASME, New York, pp 67–73
 20. Ozisik MN (1993) *Heat conduction*. Wiley, New York
 21. Parker KJ (1981) Ph.D. Thesis, Massachusetts Institute of Technology
 22. Patera AT, Mikic BB, Bowman H (1978) The effect of cylindrical probe geometry on the accuracy of tissue perfusion measurements made with the thermal diffusion probe. *ASME Bioeng Proceed* 5:157–159
 23. Penns HH (1948) Analysis of tissue and arterial blood temperatures in the resting human forearm. *J Appl Physiol* 1:93–122
 24. Scott EP, Robinson P, Diller TE (1997) Estimation of blood perfusion using a minimally invasive blood perfusion probe. In: *Advances in biological heat and mass transfer*, HTD-vol.355/BED, vol 37. ASME, New York, pp 205–212
 25. Valvano JW, Badeau AF (1987) In vivo measurement of intrinsic and effective thermal conductivity using sinusoidally heated thermistors. A technique for measuring the thermal conductivity and evaluating the ‘apparent conductivity’ concept in biomaterials. In: Sixth southern biomedical engineering conference, pp 1a–4a
 26. Valvano JW, Allen JT, Bowman HF (1984) The simultaneous measurement of thermal conductivity, thermal diffusivity, and perfusion in small volumes of tissue. *ASME J Biomech Eng* 106:192–197
 27. Valvano JW, Badeau AF, Pearce JA (1987) Simultaneous measurement of intrinsic and effective thermal conductivity. In: *ASME Winter Annual Meeting, Thermodynamics, Heat and Mass Transfer in Biotechnology*. ASME, Boston, pp 1–5
 28. Weinbaum S, Jiji LM (1985) A new simplified bioheat equation for the effect of blood flow on local average tissue temperature. *ASME J Biomech Eng* 107:131–139
 29. Yuan DY, Valvano JW, Anderson GT (1993) Measurement of thermal conductivity, thermal diffusivity, and perfusion. *Biomed Sci Instrum* 29:435–442
 30. Zhang HF, He LQ, Cheng SX, Zhai ZT, Gao DY (2003) A dual-thermistor probe for absolute measurement of thermal diffusivity and thermal conductivity by the heat pulse method. *Meas Sci Technol* 14:1396–1401
 31. Zhong SK, Wu DJ (1982) *Concise physical handbook* (in Chinese). JiangXi People’s Publishing House, Nanchang