Modeling of Systemic Circulation and Heat Exchange in Whole Body Hyperthermia (43-44°C)

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Abstract

Many experimental and clinical trials showed a high efficacy of whole body hyperthermia (43-44°C) (WBH) in treatment of malignant tumors and in some viral diseases including HIV/AIDS. However a widespread clinical application of WBH remains difficult due to poorly controlled circulation disturbances.

The aim of current research is to describe structural connections between the organs during WBH (43-44°C), and find the way to stabilize blood circulation. Current research formulates model requirements for blood circulation changes, and shows interconnections between the models of circulation and heat transfer.

Potentialities of circuit theory allow measuring of some parameters (thermal capacity and thermal conductivity of organs) in the beginning of WBH procedure when circulation is stable. Results from the model will allow predicting blood circulation disorder and their prevention when rising the body temperature over 42°C. Thus it can be use for temperature calculation, increase of efficacy and safety of hyperthermia.

1 Introduction

Recently the method whole body hyperthermia becomes widely used in medical practice. Many experimental researches on animals and people showed a high efficiency of this method in oncology, correction of immunity and virology, including AIDS-therapy [1-6].

First, according to the basic biochemical laws, the need of tissues for energetic substrates increases with the temperature [7]. Special modes of high-frequency ventilation and hyperglycemia are used for the solving of this problem. Second, it is necessary to provide availability of energetic substrates [8] - their delivery to the capillaries with the help of blood circulation and maintenance of optimal gradient of hydrostatic pressure to carry energetic substrates to tissues (and products of a metabolism - from tissues). Therefore it's very important to provide stable hemodynamics for efficiency and safety of WBH.

It is established in vitro, that apoptosis of tumor cells occurs more actively at temperature above 43°C [9, 10]. In experiments on animals it is shown, that rise in temperature of a brain up to 45°C does not result in its damage [11]. However wide application of WBH over 43°C on human is complicated due to poorly controlled hemodynamic disturbances - peripheral vasodilatation and arrhythmia. At decrease of mean aortic pressure (more exact - diastolic pressure) blood supply of a myocardium is severely disturbed. It results in decrease of cardiac output and a progressing hypotonia. The blood flow and heating of the affected tissues decrease, which reduce efficiency of hyperthermia.

Modern pharmacological agents allow influencing the various parts of hemodynamics. For an effective application of drugs it is necessary to monitor the changes of an organism in a real time mode. Thus, there is a need of forecasting of hemodynamic disturbances and correction of the dysfunctions on the basis of the exact analysis of a situation.
There are various models of hemodynamics (stochastic descriptions, models with the concentrated parameters, models with the allocated parameters), which have been focused on qualitative and quantitative interpretation of the mass transfer phenomena in a blood stream [12, 13]. In particular, some authors connect hemodynamic disturbances at WBH with reduction of blood viscosity [6]. Other researchers consider that in conditions of WBH up to 42°C the basic hemodynamic disturbances are connected to decrease of systemic vascular resistance. The further rise of body temperature results to uncontrollable vasodilatation [14]. Suggested models do not allow to predict hemodynamic changes with sufficient accuracy, occurring at WBH as do not take into account heterogeneity of changes of peripheral resistance of vessels in different organs. It is necessary to build the models which can be numerically analyzed and allow to track processes of substance and energy transfer. Results of the numerical analysis can give reliable information to assess the condition of an organism.

2 Interrelation between models of blood circulation and heat transfer

Current work shows WBH (the immersion-convectional method – heating of body in a bath with hot water) as a physical process of heat and mass transfer, namely:
I. Heat transfer is carried out by two ways:
   1) Skin ==> organs;
   2) Skin ==> blood ==> organs. At this way:
      a. Venous stream mixes the heated portions of blood from venous sinuses of a skin with colder fractions;
      b. Arterial blood transfers heat to the organs.
II. Heat transfer from arterial blood to the organs depends on a general hemodynamics and a blood flow (BF) in each organ.
III. Changes of temperature of organs results in changes of physical parameters of heart, vessels and the blood, determining the condition of hemodynamics.

Various organs are heated up with various speeds and have various temperatures during heating. The reason of it is a different thermal capacity of tissues, different BF and different weight of organs. The temperature and BF of each organ are important for the actual task.

Such requirements to model are formulated:
I. Basic elements of blood flow circuit (BFC) are the separate organs, which are characterized by a unique value of temperature and a unique value of a blood flow through the organ. If various fragments of body have essentially various temperatures (for example, heated and not heated fragments of skin) or various blood supply (for example, branching blood vessels) elements of BFC we count fragments of these organs with unique values of temperature and a blood flow.
II. BFC nodes we count points of blood flow branching. Each node with number i (i = 1, …, q) is characterized by potential - a blood pressure, $p_i$, each branch with number k (k = 1, …, n) is characterized by value $BF_k$.

III. Operating modes of elements are examined from two points of view - a thermal mode (heat transfer model) and hemodynamic mode (blood circulation model). Two interconnected models of lower level are actually examined:
   1) The thermal mode of elements is characterized by their temperature and a stream of heat;
   2) Hemodynamic mode of an element is characterized by mean aortic pressure (or decrease of arterial pressure) and BF.

IV. Connections between elements should be properly described.

The most effective method for the analysis of the processes occurring in the given model is the mathematical apparatus of the circuit theory. With the purpose of formalization of these tasks the analogies between elements of model and electrical elements are carried out. In model of blood circulation the analogue of an electric voltage represents decreasing of hydrodynamic pressure on this element. Analog of an electric current is BF. In the elementary case, heart is possible to consider as a source of blood pressure (BP) if BP is precisely known, or the source of the current if BF is known.

Resistance of a segment of a blood vessel is understood as the ratio of pressure drop to a BF. In model of heat transfer analogue of an electric voltage is the difference of temperatures. Analogue of an electric current is the heat flow. The ratio of a heat flow between the pair of elements to a difference of their temperatures represents heat conductivity. In the model of heat transfer it is also necessary to enter thermal capacities of elements. Both in the circuit theory and in a model of blood circulation, parameters of elements can depend on external influences. A temperature-dependent nonlinear resistive model should be used in forecasting of hemodynamic disturbances at WBH. The temperature is one of the essential factors, which connects two models. Those two models are connected by temperature of organs (elements) and the speed of a blood flow determining intensity of heat exchange (Fig. 1). The temperature of blood is accepted equal to the temperature of corresponding organs.

![Figure 1: Interrelation between models of blood circulation and heat transfer](image-url)
As times of temperature changes in organs are measured by minutes, all parameters of hemodynamics (BF, pulse rate) should also be measured the same scale of time. Hemodynamics can be characterized by parameters of fast processes (for example, duration of a systole, parameters of sphygmomanometry). If necessary it is possible later to use their average values. This approach was applied by other authors in modeling of heat transfer in blood vessels [15].

3  The equivalent circuit of systemic circulation

Blood circulation in each organ can be presented as a separate circuit (Fig.2).

Figure 2:  Detailed (a) and simplified equivalent (b) scheme of element

The basic regulators of vascular resistance in organs are arterioles. For simplification it is possible to present each element as one resistor. At the description of the general structure of model we will use the simplified representation of an element. At specification of element parameters dependent on temperature and other factors we will use detailed representation.

Passive elements are characterized by resistance $R_k$ or conductivity: $G_k = 1/R_k$, connecting a potential difference with BF (Fig. 3).

Figure 3: Relation between element's BF and a pressure in BFC nodes

It's clear, that:

$$I_k = \frac{(p_i - p_j)}{R_k} = \frac{(p_i - p_j)G_k}{G_k}$$  \hfill (1)

Further we will also use a matrix designation: $G = \operatorname{diag}\{G_k\}, \ (k = 1, \ldots, n)$.

Active elements are the sources that similar to electromotive force (emf) sources which can be by analogy named hydromotive force. Thus BFC fragment can be presented as sown on Fig. 4:

Figure 4: Transformation of BFC fragment with hydromotive force $H'$ and $H''$ (a) in the equivalent circuit with a source of current $J$ (b)

$H'$ and $H''$ sources represent the ideal pressure made by the left and right heart, accordingly. Elements and the way of their connection is clear from the figure, however the mathematical description of process needs a formal representation of elements connection. During the analysis this circuit can be transformed according to elementary rules. For example, at consecutive connection of several passive elements they can be replaced with one which equivalent resistance is equal to their sum. At parallel connection conductivities are summarized, instead of two active elements $H'$ and $H''$ it is possible to apply one:

$$H = (H' + H'')$$  \hfill (2)

So, here it is convenient to transform BFC fragment from 4 elements {Left heart, right heart, left lung, right lung} to a form shown on Fig. 4, b.

Formulas of transformation are simple enough here:

$$G_{\text{tungs}} = G_{\text{left lung}} + G_{\text{right lung}}$$  \hfill (3)

$$J = (H' + H'')G_{\text{tungs}}$$  \hfill (4)

Let's show a full BFC in which the basic organs participating in blood circulation system of an organism are represented (Fig. 5).

Here $n = 43$ passive elements connected with $q = 29$ nodes are represented. It is considered, that parameters of all elements and, at least, their dependences on temperature are given.
Figure 5: The circuit of blood circulation at immersion-convectional method of hyperthermia

The simple way of describing connection of elements is the table which contains a number of an element, its name and numbers of nodes to which it is connected (Table 1, fragment).

Table 1. Fragment of the table showing a connection of elements

<table>
<thead>
<tr>
<th>Element number</th>
<th>Element name</th>
<th>Node - beginning of a branch</th>
<th>Node - end of a branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>muscles1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>skin1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>Heart</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>43</td>
<td>bones2</td>
<td>29</td>
<td>28</td>
</tr>
</tbody>
</table>

For the description of algorithm of the mathematical analysis of a task used the incidence matrix $A = \{a_{ik}\}$ (the size $(q-1) \times n$), which rows correspond to BFC nodes (except one), and columns correspond to branches (elements). Here $a_{ik} = 0$ if the branch $k$ is not connected to node $i$, $a_{ik} = 1$ if the branch $k$ is attached to node $i$ by the beginning, and $a_{ik} = -1$ if the branch $k$ is attached to node $i$ by the end. In this case the description of a task of BFC analysis goes to the matrix equation:

$$A'AGP = AJ \quad (5)$$

Here $A'$ - transposed matrix $A$;

$P = \text{col} \{p_1, \ldots, p_{(q-1)}\}$ - a vector of main blood pressures;

$J = \text{col} \{J_1, \ldots, J_n\}$ - a vector of main currents considered in the task (only $J_6 \neq 0$, other $J_i = 0$);

$G = \text{diag} \{G_k\}$, $(k = 1, \ldots, n)$.

The solving of this system concerning the required vector $P$ is simple:

$$P = (A'AG)^{-1}AJ \quad (6)$$

and we will receive distribution of a blood flow $I = \text{col} \{I_1, \ldots, I_n\}$ in BFC elements as:

$$I = G'P \quad (7)$$

4 The equivalent circuit of heat transfer

Construction of the equivalent heat flow circuit (HFC) in methodical sense is similar to the previous constructions, but it is more difficult. The task of heat transfer analysis is reduced to calculation of temperatures of elements. Here it is necessary to use concepts of a thermal capacity of organs $C_k$, and the heat flow $Q$ to organs. As potential function the temperature of organs $T_k$ $(k = 1, \ldots, n)$ is used.

At immersion-convectional method of hyperthermia there are 3 ways of heat exchange of an organism with environment:

1) heat exchange of the skin heated with hot water (a body immersed in a bath);
2) heat exchange of not heated skin with air;
3) heat exchange through breathing.

Preliminary calculations show, that the first factor plays the greatest role in process of hyperthermia, and two others can be neglected.

Physical processes of heat exchange in each element can be presented by following the scheme (Fig. 6).
These processes correspond to the local equivalent circuit (Fig. 7).

HFC nodes correspond to the nodes (organs) with some temperatures. If the amount of elements in BFC equals \( n \), then it is necessary to enter fictitious node with zero temperature. Moreover we’ll add an environment – the hot water with known temperature, as a separate node. Taking into account heat exchange of a body with air, it is also necessary to present air as node with known temperature.

HFC branches are ways of a heat transfer. For this purpose it is necessary to use the information about BF in element and about the area of thermal contact of an element with the surrounding elements. The equation of thermal balance in node \( k \) will be the following:

\[
C_k \frac{dT_k}{dt} = \sum_{v} G_{vk}^h (T_v - T_k) + Q_{sk} - Q_{ak}
\]

Here \( C_k \) – a thermal capacity of an element \( k \);
\( T_k, T_v \) – temperature of elements with numbers \( k \) and \( v \), accordingly;
\( G_{vk}^h \) – heat conductivity between elements \( k \) and \( v \), having the area of thermal contact \( S_{vk} \);
\( \alpha_{vk} \) – coefficient of heat transfer, in a first approximation it is possible to count it the same for all elements;
\( Q_{ak} = c_{ak} T_r \) – quantity of heat, brought to an element \( k \) from an element \( r \) with arterial blood;
\( c \) - a thermal capacity of blood;
\( Q_{sk} = c_{sk} T_s \) - the quantity of heat which is left away from an element \( k \) with venous blood.

The Eq. (8) can be the following:

\[
C_k \frac{dT_k}{dt} = \sum_{v} G_{vk}^h (T_v - T_k) + \alpha_{vk} S_{vk} T_v + I_k T_r
\]

(9)

It’s clear, that both the members of type (c I k) and type (\( \alpha_{vk} \), \( S_{vk} \)) represent heat conductivities, and we will further use a generalized designation \( G_{vk}^h \); we’ll calculate this volume using a physical meaning of heat transfer. Now, generalizing this equation, we’ll spell it in the matrix form:

\[
C \frac{dT}{dt} = G^h T + J^h
\]

(10)

Here \( T = \{T_1, ..., T_n\} \) – a column matrix of temperatures of elements;
\( C = \text{diag} \{C_k\}, (k = 1, ..., n)\);
\( G^h = \{G_{vk}^h(I_k)\} \) – a matrix of main heat conductivities of the size \( n \times n \);
\( J^h = \{J_1, ..., J_n\} \) – a column matrix of main heat sources, showing a body heating by water (and, perhaps, cooling by air).

To the differential Eq. (10) it is necessary to add initial conditions – values of temperatures of organs at \( t = 0 \), \( T(0) = T_0 \), for example: \( T_k = 36.6^\circ C \) (\( k = 1, ..., n \)).

5 Organization of process of calculations

On the basis of Eq. (5) and (10) it is possible to organize iterative process of calculations. On the one hand, parameters of BFC model depend on temperature of organs, on the other hand – parameters of HFC model depend on distribution of blood flow BF. A doctor conducting procedure of hyperthermia is interested in the prognosis of BF and BP. The models received allow to enter real values measured in hyperthermia process (temperature, pressure and other parameters) into process of calculation and to correct model in real time mode.

It is necessary to stress, that there are only the basic (structural) relations between variables shown. For the correct solving of tasks it is necessary to have data on a plenty of parameters of each patient. Some of them (weight, volume, a blood flow in different organs) can be measured during preliminary anthropometrical, tomographic and ultrasound examinations. It is possible to use the rules of blood flow changes received during a practical application of hyperthermia [16]. Definition of all coefficients, allowing authentic numerical calculations, can be made by the principles and methods of diagnostics and theory of electric circuits [17]. The model suggested will allow determining some parameters (a thermal capacity and heat conductivity of organs, dynamics of a blood flow in organs) during WBH procedure at the initial stages of warming, at stable hemodynamics. While rising the temperature over 42 in body the usage of the received parameters will enable...
forecasting and prevention of hemodynamic disturbances, calculation of temperatures, increase of efficiency and safety of hyperthermia.

References


