Hypothermic Brain Protection Strategies using Thermal Models

by

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Abstract

The brain is the organ at greatest risk of injury during periods of reduced blood flow; to prevent tissue death and protect organ function in such conditions, hypothermia is used. The primary goal of this research is to use a thermal model as a tool to develop and optimize hypothermic protection methods for the brain tissue given the fact that the cooling time, as well as the degree of temperature reduction required for successful outcome are still uncertain, and the knowledge of brain temperature is desirable during clinical treatment, but highly destructive.

To improve the existing thermal models of brain, the effect of the temperature over the metabolic heat generation, and the regulatory processes that control the cerebral blood perfusion were incorporated in this project. The proposed thermal model was validated using data obtained from experiments of perinatal asphyxia, and different cooling strategies on swine. The temperature calculations show the same behavior and tendencies observed experimentally, and the importance of accurate thermal properties and anatomy in the temperature prediction is observed.

Based on these observations, a realistic geometric model of the human head obtained from tomographic data was created to study cooling and rewarming during brain ischemia produced by circulatory arrest and stroke. The calculations performed have helped to understand the importance of the tissue temperature gradients in the success of hypothermic therapies. The calculations show that hypothermic cardiopulmonary bypass (CPB) together with external head cooling help reduce the tempera-
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Chapter 1

Introduction

This thesis deals with thermal modeling of the human head. The primary goal of this research is the development of protection methods for the brain tissue through the use of hypothermia. This research will be useful in the refinement of cooling techniques used in the treatment of brain injury, ischemia and asphyxia. This dissertation is based on the fact temperature reduction after brain injury or cerebral stroke is known to provide neuroprotection due to metabolic reduction and suppression of the inflammatory response; but the cooling time, as well as the degree of temperature reduction required for successful outcome are still uncertain.

Brain temperature depends on three major factors: local heat production, cerebral blood flow, and the temperature of the blood perfusing the tissue. Studies have shown that in general a direct correlation between rectal temperature and brain temperature exists [78], but during hypoxia or hypoxia-ischemia, brain temperature falls and a dissociation between brain temperature and systemic temperature is observed [35, 37]. As a result, monitoring only body temperature is not enough to infer the actual temperature status of the brain nor the efficiency of therapeutic management [75]. The measurement of brain temperature is an invasive procedure and it is justified only in patients that undergo cranial surgery [50], or which have neuro-surgical conditions necessitating other invasive procedures such as intracranial pressure monitoring. In the clinical setting, there is no accepted means to non-invasively monitor brain temperature. As a result, the development of thermal models that incorporate organ physiology and external temperature measurements is extremely useful and important due to the therapeutic implications of temperature control as a res-
cue strategy and tin the analysis of the existence of an optimal time window for hypothermic treatment [65, 31, 70, 19].

The calculations presented herein, simulate the temperature variations observed during conditions that affect the cerebral blood flow, such as asphyxia, circulatory arrest and stroke. The calculations incorporate experimental measurements of blood flow, metabolic activity and body temperature registered during such conditions. The proposed thermal model is also used to simulate different cooling strategies that correspond to selective head cooling (SHC) and whole body cooling (WBC) during periods of abnormal cerebral blood flow and metabolism, and the effect of such cooling techniques in the brain temperature distribution are studied.

Before introducing the thermal model used and the results obtained from it, Chapters 2 and 3 describe the concepts and theory behind heat transfer in living organism and the mechanisms that regulate tissue blood flow. Chapter 2 deals with heat balance in organisms, the physiological and environmental factors that affect the tissue temperature, the effect of temperature alterations in animals, and how such temperature variations can be applied in clinical therapies. This chapter also covers the factors affecting tissue temperature, the way in which such factors are incorporated in thermal models, the classification of thermal models, and their applicability. Given the fact that blood flow and metabolic activity are important factors in determining the tissue temperature, Chapter 3 presents the parameters that affect the cerebral blood flow, and a classification of the mathematical models used to describe it. This chapter also discusses the effects of cerebral blood flow reductions and how temperature affects the evolution of brain injury produced by lack of blood flow (ischemia).

Chapters 5 to 7 include the results of the calculations using the thermal model described in Chapter 4. The results are divided in two major groups that correspond to the calculations using the layered model described in Section 4.2, and the calculations using the realistic geometry model of Section 4.3. The layered head model was used as a first approximation to determine the important factors affecting brain tempera-
ture; and after validating the model against direct brain temperature measurements (Chapter 6), the importance of realistic geometry was observed.

Chapter 5 shows the temperature calculations using the geometrically simplified or layered model. The results correspond to the steady state temperature distribution within the different tissue layers for different external boundary conditions and values of the physiological parameters (MABP, $PaCO_2$, and $PaO_2$) that affect the cerebral blood flow. This chapter also analyzes the effect of different cooling and rewarming strategies on the brain temperature distribution before and after circulatory arrest in adults and children.

In Chapter 6 the numerical calculations of the brain temperature in swine using the layered head model are presented. The calculated temperature distribution is validated against the in-vivo temperature measurements, and from the comparison with the calculated temperature it was observed that accurate knowledge of parameters such as the skin and bone thermal conductivity and the system geometry are necessary for effective thermal modeling.

Chapter 7 presents brain temperature calculations using the realistic 3d-model of the human head and neck (Section 4.3) for the cases of global and local blood flow variations and the application of hypothermic therapies during conditions of abnormal blood flow and metabolism produced by asphyxia, hemorrhage, circulatory arrest or stroke. The results of this study can be used to analyze the transient temperature in the brain tissue to improve the application of hypothermia in the treatment of cerebral ischemia. Finally, conclusions and a description of future work are given in Chapters 8 and 9, respectively.
Chapter 2

Temperature and Heat Balance in Humans

Body temperature in mammals and other homeotherms is maintained within a fairly constant range that is compatible with other regulatory systems and cellular physiology. Temperature regulation in animals implies the presence of mechanisms capable of level the rate of heat production to the rate of heat transfer to the environment. In mammals, chemical energy obtained from foods is converted into heat to support cellular processes and maintain body temperature. Analogously, heat can be lost to the environment by conduction, convection, radiation and evaporation. The rate of heat transfered by each one of these modes depends on the surface area, and the temperature difference between skin and the external medium.

The heat balance equation for the case of constant mean body temperature for a resting subject is

\[ S = MR - W - E - C - K - R, \]  \hspace{1cm} (2.1)

where \( S \) corresponds to the rate of storage of heat in the organism, \( MR \) is the rate of metabolic energy transformed in heat, \( W \) is the rate of work done by the organism, \( E, C, K \) and \( R \) denote the rate of evaporative, convective, conductive and radiant heat transfer from the organism to the environment, respectively. The quantities in equation (2.1) are commonly expressed in terms of body surface area \( Wm^{-2} \) or body mass \( Wkg^{-1} \).

Temperature regulation is the result of evolution, and it helps to optimize organ function, it is also an important factor in the development of infection diseases. Some thermoregulatory mechanisms observed in homeotherms are shivering, sweating, panting and selective brain cooling (SBC). These thermoregulatory mechanisms
Figure 2.1: Illustration of thermoregulatory thresholds in unanesthetized and anesthetized humans. Adapted from [51].

are the result of metabolic and blood flow changes controlled by the thermostatic region of the hypothalamus. Fig 2.1 shows the temperature range at which these regulatory mechanisms occur in humans and the effect of anesthesia on their onset.

Shivering increases heat production in muscle tissue by producing involuntary muscular contractions, as a result the skeletal muscle temperature raises. During sweating and panting, heat is lost by evaporative heat transfer. Conversion of water from liquid to vapour is an endothermic process, evaporation occurs when the water vapour pressure on the skin is greater than that of the surrounding air. In sweating vasodilatation of the cutaneous vessels is observed, and the blood volume supplying the skin is cooled by surface evaporation; the sweating rate of humans is of the order of 10 to 15 grs of $H_2O/\text{min m}^2$, and the latent heat of vaporization is approximately 40 W for 1 gr of $H_2O$ per minute. Panting, on the other hand is characterized by a sharp increase in the respiration rate, and the evaporation of water in the nasal passages, mouth and lungs, which results in cooling. Finally, SBC is based on the heat exchange between venous return and arterial blood, and it is strongly dependent on the geometric distribution of large blood vessels. In several mammals such as cats, sheep, dogs, antelopes, and reindeer, there exists a special vascular arrangement,
called *rete mirabilis*, that brings warm carotid arterial blood and cool jugular venous blood to close contact, enabling countercurrent heat exchange. However, there are some other organisms such as squirrel monkey, rabbit, rat, and guinea pigs, which lack the rete, and yet achieve intensive heat loss in their brain by thermal panting or sweating.

In the moderate hyperthermic human head, heat loss by sweating is between 125 and 175 W, and approximately 100 W are lost due to water evaporation in the upper airways [10]; these measurements together with the fact that humans have survived rectal temperatures of up to 47 °C [58], has awaken the idea that SBC takes place in humans even though no rete is present and panting does not occur. To determine whether sweat evaporation combined with vasodilatation is sufficient to achieve brain cooling during various stress conditions, or if heat loss from the upper respiratory tract should be considered; several authors [10, 8, 58, 94, 60, 68] have used the available biological thermal models to calculate the temperature distribution in simplified anatomical models of a human head; however, none of these studies have been conclusive. Recent deep temperature measurements in subjects undergoing cranial surgery [50] strongly suggest that SBC occurs in humans, but a better understanding and model implementation is needed.

### 2.1 Deviations of the Average Temperature and its Applications

Extreme temperature variations in homeotherms can be lethal, and range from heat stroke to coma induced by cold exposure. At the cellular level, a small temperature reduction can decrease the tissue oxygen requirements, and temperatures over 42 °C can produce protein break down. As a result, temperature reduction in cases of low blood flow and the use of high temperatures to promote necrosis of specific tissues have promising clinical applications, but require ample physiologic knowledge of temperature control and tissue heat transfer mechanisms.
The idea of using controlled temperature induced variations in homeotherms to fight disease is not new, and the efforts and possible applications of hyperthermia or temperature increases over the normal range and hypothermia or body temperature reduction are described below together with the clinical applications of such therapies. However, to successfully apply either hyperthermia or hypothermia in any medical treatment it is necessary to achieve fine temperature control, for which studying heat transfer in tissues is necessary. The efforts in this direction are described in the following section.

2.1.1 Hyperthermia

Deliberately induced hyperthermia (raised body temperature) as a means for healing has been known since Hippocratic times. Indeed, our bodies will develop a fever as part of a strategy for overcoming infections. Greeks, Romans and Chinese used thermal baths to treat rheumatism and joint illnesses. In the late 19th Century physicians and scientist began studying the effect of hot baths after observing shrinkage of tumors and healing of diseases like Leprosy and Syphilis. Studying the apparent cure of Syphilis after febrile episodes, and the gave the Nobel prize to Dr. Wagner-Jauregg in 1927. During the sixties physicians started using local hyperthermia to treat sarcomas, and some cases of cervix cancer. Today, the interest on localized hyperthermia to treat tumors remains, but also whole body hyperthermia has been used to kill cells infected with viruses, such as HIV and Hepatitis C.

Hyperthermia refers to core temperatures greater than 38°C, and it is applied in cancer treatment, because neoplastic tissues and vasculature are less resistant to thermal stresses than the normal cells [74, 33, 63]. In addition, tumours have an impaired ability to adapt their blood circulation to the effects of high temperatures and extreme hyperthermia can, therefore cause an actual reduction of blood flow within a tumour. On the other hand, certain chemotherapy agents are known to be more effective in a hyperthermic environment and can be usefully combined with this
treatment. This can lead to beneficial results with lower dosage regimes than usual and consequently with fewer side effects.

To successfully apply whole body or localized hyperthermia in cancer treatment, a fine temperature/heat-dose control is required, which implies the knowledge of temperature distribution in the tumor and the healthy surrounding tissue as well as the development of heat generation and delivery techniques that allow minimization of thermal damage to healthy tissues [26]. Among the heat generation techniques used to produce interstitial hyperthermia one finds radio frequency (RF) techniques where, a voltage is applied between microelectrodes inserted into and around a tumor; Microwave techniques, where needle like antennas operating in the range of 300 to 2450 MHz are implanted into the cancerous tissue; inductively heated "seeds" of ferromagnetic material implanted in the tissues; and several other heating techniques based entirely upon heat transfer mechanism present within the tissues, for instance heating of external tissues using electrical heaters or hot water radiators. Other applications of hyperthermia are for the treatment of chronic inflammatory conditions such as ulcerative colitis and Crohn’s disease, rheumatic conditions, bronchial asthma, chronic and recurrent viral infections, and in conditions requiring detoxification

2.1.2 Hypothermia: Importance and Problems

The reduction of body temperature has also proven to be a useful therapy in some circumstances. The reduction of temperature is referred as hypothermia, and depending on the temperature drop it is classified as: early, mild, severe or profound [51], as shown in Table 2.1. The use of mild hyperthermia began after 1970 in cardiac (cardiopulmonary bypass), neurosurgical (cerebral aneurysm surgery) and vascular (aortic surgery) surgery. The interest of hypothermia arose because it was observed that temperature reduction increased the tolerance of brain and spinal cord to ischemia, and reduced the rate of mortality and morbidity [83]. However, contradictory results have been observed, and careful study of cooling and rewarming techniques is still
Table 2.1: Stages in Hypothermia

<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>Core Temperature</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>35 – 36°C</td>
<td>Vasoconstriction and shivering</td>
</tr>
<tr>
<td>Mild</td>
<td>32 – 35°C</td>
<td>Vital signs increased</td>
</tr>
<tr>
<td>Severe</td>
<td>17 – 28°C</td>
<td>Coma, cardiac instability</td>
</tr>
<tr>
<td>Profound</td>
<td>4 – 17°C</td>
<td>Apnea, cardiovascular collapse, coagulopathy</td>
</tr>
</tbody>
</table>

necessary.

The interest on the effects of temperature reduction in living organisms and tissue began in the early 1900’s with the study of hibernation and the attempts to exploit this phenomenon clinically [67]. Since the 70s to the present day, it has been observed a reduction in mortality rate when core temperature is decreased during surgery; however, it is also a well known fact that hypothermia can lead to death. The onset of hypothermia begins with shivering, cold hands and feet, then numbness. It progresses to drowsiness, mental confusion, reduced heart rate and finally unconsciousness, as observed in Table 2.1.

Brain temperature has been recognized as a strong factor in the treatment of brain injury [35, 37, 15], it affects the release and absorption of substances such as metabolites and oxygen. Multiple experiments show that modest or moderate hypothermia provides neuroprotection during and after ischemia [9, 16, 34, 7], and that an increase in brain temperature has a deleterious effect in the setting of hypoxia-ischemia or ischemia because it exacerbates the extent of brain injury compared to normothermic conditions [55].

The advantages of hypothermia during hypoxia and ischemia are the reduction of the metabolic activity and the tissue oxygen requirements, the possibility to reduce
increased cardiac output and ventilation observed during hypoxia, and the suppression of inflammatory mechanisms that trigger febrile responses. On the other hand, a rapid decrease in body temperature can produce shivering and increase metabolic activity, reducing the beneficial effects of hypothermia. Also, oxygen transport is observed to be impeded at very low temperatures limiting hypothermia to temperature reductions of a few degrees [78]. Some other problems of hypothermia are the rewarming strategy and the methodology to initiate cooling[20].

2.2 Heat Transfer in Tissues

The study of the heat transfer processes that occur in biological tissues is applied to develop temperature control during hypothermia and hyperthermia; to estimate the temperature distributions in core organs or deep tissue structures where direct temperature measurement results highly invasive; to determine changes in organ temperature due to energy deposition of electromagnetic waves produced by radars, handheld telecommunication devices or imaging techniques; to understand the thermoregulatory mechanisms in living organism; and in some clinical applications like analysis of burns, cryosurgery; and measurement techniques of tissue thermal properties.

The development, improvement and use of biological thermal models has important applications in several areas of medicine, such as surgery, anesthesiology and treatment of brain injury to improve neuroprotection after hypoxia or ischemia. Thermal models can be used to determine accurate temperature distributions in deep organ structures based on superficial temperature measurements. These models can also be used in the optimization of hyperthermic therapies, in treatment of hypothermia in infants; in the evaluation of possible health hazards caused by electromagnetic energy deposition; and, in evaluation of noninvasive measurement techniques.

To achieve an accurate thermal description of an organ or tissue, the specific metabolic processes, blood flow, and thermoregulatory mechanisms occurring at the tissue should be considered; To do that, a detailed anatomical study of the organ is
Table 2.2: Variations in blood flow, and metabolic rate in different organs for humans, values taken from Ref. [27]

<table>
<thead>
<tr>
<th>Organ</th>
<th>Mass (Kg)</th>
<th>Blood flow (ml/min)</th>
<th>Metabolic rate (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>0.3</td>
<td>250 - 1800</td>
<td>10-31</td>
</tr>
<tr>
<td>Liver</td>
<td>2.6</td>
<td>1500</td>
<td>18</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.3</td>
<td>1260</td>
<td>6</td>
</tr>
<tr>
<td>Brain</td>
<td>1.4</td>
<td>750</td>
<td>17</td>
</tr>
</tbody>
</table>

necessary. The anatomical study will determine the characteristic vasculature, and consequently the presence of countercurrent vessel pairs and evaporative surfaces that affect the organ temperature.

2.2.1 Heat Generation, Storage and Transport Processes

In any organism energy is necessary to sustain processes such as muscular activity, secretion, maintenance of membrane potentials, and synthesis of substances. Such energy is obtained from food ingestion, however only about 25% of the energy stored in the food is available for cellular use, the rest is turned into heat. Heat generation depends on the activity level of the organism and varies in different organs as seen in Table 2.2. The heat generated as a result of cellular metabolism is distributed in a complex fashion. Removal of the heat, on the other hand, is controlled passively by the thermophysical properties of the tissues, and actively by blood flow and the geometry of the vascular structure.

Among the factors to be considered when developing a basic model to describe the thermal state of an organism are:

1. Geometry of the organ or tissue in consideration
2. Heat capacity or thermal inertia of the tissues involved

3. Conduction of heat due to temperature gradients in the tissue

4. Heat production due to metabolic processes

5. Role of blood flow in the transfer of heat between tissues and between tissue and environment

6. Thermoregulatory mechanisms and physiological responses of an organism to different thermal stresses

7. Thermophysical properties of tissues and their variations with the temperature

8. The interaction with the environment

2.2.2 Thermal Models of Living Tissue

To advance in the understanding of heat and mass transfer processes that occur in a living organism, several mathematical models have been proposed [64, 76, 91, 92, 13, 87, 88, 86, 11, 89, 2]; these models are based on the energy conservation at the tissue level, and the application of constitutive laws. However, thermal energy transport in living tissue is extremely difficult to model, due to tissue heterogeneity; convective effect added by the vasculature; simultaneous heat transfer processes occurring in the tissue, such as conduction, convection, radiation, and evaporation; species to species variability of tissue thermal properties; as well as the difficulty encountered in the in-vivo measurement of tissue thermal properties.

Consideration of organ anatomy and physiology are essential characteristics in the development of thermal models, because anatomy and physiology define blood flow and metabolic activity. Finally, the consideration of thermoregulatory mechanisms such as sweating, shivering, panting, and the change in the hydraulic resistance of blood vessels is also important, but more complex to model.
Figure 2.2: Changes in the blood flow in the skin and muscle of SD rats heated with water bath. The blood flow was measured at the end of the heating period using radioactive microspheres [63].

The presence of the circulatory system is the most important characteristic of a biological tissue because it adds convective heat transport to the other thermal characteristics governing tissue heat transfer, such as conduction and heat capacitance. Experimental observations [63] have shown that when the temperature of a healthy tissue is increased, the blood flow increases rapidly, and then falls when the tissue temperature surpasses a critical threshold temperature which depends on the tissue type. For skin and muscle this threshold temperature is of 44°C and 45°C, respectively as can be seen in Fig. 2.2.

Blood circulation is strongly dependent on physiology, organ anatomy and vasculature, and when including the effects of blood flow in the thermal modeling of tissue, two different factors should be considered: blood vessels change its diameter size as they branch out; and second, there are fundamental vascular structures which appear in tissues or organs. Depending on its diameter, blood vessels are classified
as arteries, arterioles, capillaries, venules and veins (Table 2.3). Arteries and veins have diameters of the order of millimeters, and after several branching generations reduce their diameter to hundreds of micrometers to become arterioles and venules, respectively; finally, when arterioles and venules branch out they form what is called the capillary bed, which is a complex network of blood vessels that have a diameter of few micrometers. Table 2.3 shows the vessel radius, thermal equilibration length $x_{e_j}$ and the ratio between vessel length $l_j$ and $x_{e_j}$. The thermal relaxation length $x_{e_j}$ represents the distance inside the vessel that the blood needs to travel in order to equilibrate its temperature to that of the tissue. The thermal equilibration is complete when the temperature difference between blood and tissue is reduced to $\frac{1}{e}$ of its initial value. The thermal equilibration begins at the terminal arteries and veins, and it is widely accepted that equilibration takes place at the arteriole and venule levels (precapillary beds).

Because blood in vessels of diameters greater than 300$\mu$m flows at high velocities (13 – 8 cm/s) and requires to travel long distances before reaching thermal equilibration; then blood flow in the large vessels can be treated macroscopically as a nonbiological fluid in a tube buried in a solid interchanging heat with its surroundings. In this case, as shown in Fig. 2.3, three main structures are distinguished: single vessel surrounded by a tissue cylinder, artery-vein countercurrent exchange, and cutaneous vein near a surface subject to heat exchange. The heat transfer analysis on these structures is necessary to estimate cooling effects of individual vessels during local hyperthermia, or to determine possible cooling effects of vessels configurations, such as retes.

On the other hand, to deal with the thermal effects of the microvasculature, several thermal models referred as bioheat equations have been proposed, some of these are presented in Table 2.4. The main difference between these models is the required knowledge of geometrical properties of the vessel network.

The distinction between macro and micro vasculature is important depending
Table 2.3: Properties of Vascular Compartments

<table>
<thead>
<tr>
<th>Generation</th>
<th>Vessel</th>
<th>( r_i ) (( \mu m ))</th>
<th>( x_{ej} ) (m)</th>
<th>( l_j / x_{ej} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aorta</td>
<td>5000</td>
<td>190</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>Large artery</td>
<td>1500</td>
<td>4</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>Arterial branch</td>
<td>500</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>Terminal branch</td>
<td>300</td>
<td>0.08</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>Arteriole</td>
<td>10</td>
<td>5X10^{-6}</td>
<td>400</td>
</tr>
<tr>
<td>6</td>
<td>Capillary</td>
<td>4</td>
<td>2X10^{-8}</td>
<td>6000</td>
</tr>
<tr>
<td>7</td>
<td>Venules</td>
<td>15</td>
<td>2X10^{-6}</td>
<td>800</td>
</tr>
<tr>
<td>8</td>
<td>Terminal vein</td>
<td>750</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>9</td>
<td>Venous branch</td>
<td>1200</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>Large vein</td>
<td>3000</td>
<td>5</td>
<td>0.04</td>
</tr>
<tr>
<td>11</td>
<td>Vena Cava</td>
<td>6250</td>
<td>190</td>
<td>0.002</td>
</tr>
</tbody>
</table>

For a blood vessel in the \( j \)-th branching generation, \( r_j \) and \( l_j \) represent the vessel radius and length, respectively; and \( x_{ej} \) denotes the thermal equilibration length.

[13]
Table 2.4: Bioheat Transfer Models

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Applicability (vessel diameter mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennes [64]</td>
<td>Single equation, Capillary diffusion depicted by source like term</td>
<td>0.3</td>
</tr>
<tr>
<td>Chen and Holmes [13]</td>
<td>Single Equation</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td></td>
<td>Modified perfusion term + convective term + perfusion conduction term</td>
<td></td>
</tr>
<tr>
<td>WJL Model [88]</td>
<td>3-layer model, 6 coupled equations, Incomplete countercurrent equilibration</td>
<td>0.3</td>
</tr>
<tr>
<td>WJ Model [86]</td>
<td>Single equation, Effective tensor conductivity dependent on vascular geometry</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Figure 2.3 : Representative vessel-tissue interactions [87]

on the vasculature type and relative size of the tissue of interest. For instance, structures like limbs, fingers or the neck contain countercurrent artery vein pairs. On the contrary, in highly perfused tissue such as liver, kidney or brain, there are regions far away from the arteries and veins, which have capillary beds as their main structure. Since the present study focuses on brain, a bioheat type equation will be used, but for completeness a summary of works on heat transfer in macrovessels is presented in Appendix A.

Bioheat Equation

One of the oldest tissue thermal models, but the most widely used due to its simplicity was developed by Pennes in 1948 [64]. To determine the average tissue temperature
(T), Pennes modeled the tissue as an isotropic homogeneous conductor with constant thermal conductivity \(k_t\), which has two heat generation sources, one due to the metabolic heat \(q_m\) produced by the tissue and assumed constant, and the other due to the heat transferred from blood to tissue \(q_b\). So the energy equation had the form

\[
\rho_t C_t \frac{\partial T}{\partial t} = k_t \nabla^2 T + q_b + q_m,
\]

(2.2)

where \(\rho_t\) and \(C_t\) represent the density and heat capacity of the solid tissue.

Using Fik’s law, Pennes proposed that the rate of heat transferred from blood to tissue \(q_b\) can be represented by a non-directional heat source term of the form:

\[
q_b = \rho_b C_b \omega_b (T_a - T_v),
\]

(2.3)

where \(T_a\) and \(T_b\) correspond to the arterial and venous temperatures, and \(\omega_b\) is a constant representing the blood perfusion or the rate at which the quantity of blood in a given mass or volume is replenished, and is a free parameter which can be determined by curve fitting with the experimental temperature measurements.

Pennes’ primary premise was that the energy exchange between blood vessels and surrounding tissue occurs across the capillary bed, where the blood velocity is very low; therefore, one approximates that

\[
T_v = T,
\]

at the capillary level, this assumption physically implies that the arriving blood undergoes a nearly instantaneous thermal equilibration, and that the venous blood is at the average tissue temperature.

The Pennes bioheat equation was commonly used until the 70’s and 80’s when several authors ([91, 92, 13, 87]) pointed out that the capillary perfusion is not isotropic, the arterial temperature varies during vessel branching; and that Pennes equation does not account for artery-vein counter-current heat exchange, or the directional convective mechanism of heat transfer due to blood flow. And, it is nowadays recognized that the main thermal equilibration occurs in the pre- and post- capillary
vessels instead of the capillary bed. However, as long as temperature measurements are performed far away of large vessels, equation (2.2) gives reasonable results.
Chapter 3

Cerebral Blood Flow and Physiology

The present chapter is introduced in this report because of the important effect that blood flow has on the tissue temperature, and the need to determine the factors that affect the blood flow during and brain injury. This chapter describes the parameters that affect the cerebral blood flow, as well as the relationships and mathematical models that describe the cerebral blood flow given variations in some physiological parameters. The effect of temperature in the blood flow and metabolism of brain is also discussed, and it is importance in the intracranial homeostasis [69] is presented. Finally this chapter describes cerebral ischemia, which is produced by conditions like asphyxia, drowning, stroke, circulatory arrest or brain edema, and the protective mechanisms observed when body temperature is reduced during or after cerebral ischemia.

3.1 Cerebral Autoregulation

The adult brain weights between 1.5 and 1.7 kg, and has an average blood flow of 750 mL/min or 50 to 55 mL/100 g of brain/min. This blood flow corresponds to 15% of the total cardiac output for a resting individual, and even though the brain has a mass of 2% of the total body weight, it uses about 20 percent of the oxygen consumed by the whole body. The continuous requirement of blood and oxygen result form the fact that brain and spinal cord lack of stored reserves, have high metabolic activity and are less capable of performing anaerobic respiration. Given the functional importance of the brain and spinal cord, there exist regulatory mechanisms that ensure constant blood supply to these tissues. Such blood flow regulation mechanisms are the result
Table 3.1: Disturbances and vascular effectors regulating CBF.

<table>
<thead>
<tr>
<th>Disturbances</th>
<th>Vascular effectors</th>
<th>Way to eliminate the disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in PP</td>
<td>Major brain arteries</td>
<td>Vasoconstriction during increase of PP and vice versa</td>
</tr>
<tr>
<td>Increase in CBV</td>
<td>Major brain arteries</td>
<td>Constriction of CBF and/or release of CSF</td>
</tr>
<tr>
<td>Inadequateness in blood supply to tissue</td>
<td>Minor arteries</td>
<td>Vasodilatation during blood deficiency and vice versa</td>
</tr>
<tr>
<td>Shift in $P_{O_2}$ and $P_{CO_2}$</td>
<td>Minor and major arteries</td>
<td>Vasodilatation during drop of $O_2$ and rise of $CO_2$</td>
</tr>
</tbody>
</table>

of evolution, and are present in other highly perfused organs such as liver and kidney.

The term *cerebral autoregulation* describes a process by which the arterial wall stiffness is modified to maintain constant cerebral blood flow despite variations in blood pressure. Such mechanisms act to maintain relatively constant oxygenation of cerebral tissue and to ensure organ protection. The vessels involved in the control of organ blood flow are the peripheral arteries, given their thick muscular coating, which permits dilation or constriction of the vessel radius as a result of changes in concentration of ions, vasoactive substances or hormones. In the brain, the vasoactive substances are released by neurons depending on their metabolic activity. Table 3.1 shows a list of some major disturbances of the cerebral circulation, and the regulatory response of the vessels.

Brain autoregulation helps keep CBF, cerebral blood volume (CBV) and Cerebral
perfusion pressure (CPP)* constant despite changes in the systemic arterial blood pressure (MABP), and also keeps up the CFB depending on the tissue level of activity. The autoregulation of CBF is a protective mechanism that ensures delivery of oxygen and glucose to brain tissue to fulfill metabolism and maintain regular organ function. The main objective of the blood flow regulation of is to avoid hypoxia, ischemia, and capillary damage in the CNS.

When cerebral blood flow falls below 50%, physiological and electrical functions of neurons are affected and nerve communication is interrupted. For instance, when the CBV increases, some venous blood or CSF must escape to avoid a rise in the ICP; this process stops when venous sinuses are flattened or there is no CSF remaining in the head. High ICP impedes cerebral perfusion, which decreases CPP and produces ischemic damage. When CPP is inadequate, the oxygen saturation of jugular venous blood falls as a result of increased oxygen extraction from the arterial blood as it passes through the capillaries.

The autoregulation maintains CBF only for mean arterial blood pressures (MABP) between 50 and 150 mm Hg. When MABP falls below 50 mm Hg, vasodilatation becomes inadequate and ischemic brain damage occurs; on the other hand, if the MABP rises above 150 mm Hg, constriction falls, and cerebral hemorrhage, brain edema or cerebral vasospasm may occur. Several clinical factors affect MABP and CPP, such as: asphyxia, brain lesions, stroke, chronic sickness like hypertension and diabetes; and infections like meningitis. In Table 3.2, the normal values of ICP, CPP and MABP in the brain are displayed. Loss of cerebral autoregulation mechanisms is observed a number of medical conditions, one important example being head trauma, ischemia during circulatory arrest or stroke or severe hypothermia.

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*The perfusion pressure is the effective pressure driving blood through and organ. In the brain, the CPP is defined as the difference between the mean arterial blood pressure (MABP) and the intracranial pressure (ICP). This last refers to the pressure within the rigid skull.
Table 3.2: Normal pressure values within the brain.

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Value (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP</td>
<td>50-150</td>
</tr>
<tr>
<td>CPP</td>
<td>80</td>
</tr>
<tr>
<td>ICP</td>
<td>5-13</td>
</tr>
</tbody>
</table>

3.1.1 Physiological Parameters that Affect the Cerebral Blood Flow

The factors that trigger the variation in the vessel caliber occurring during autoregulation are changes in physiological parameters, such as, the mean arterial blood pressure (MABP), the partial pressure of oxygen and \( CO_2 \) in the arterial blood (\( P_{O_2} \) and \( P_{CO_2} \)), the tissue pH and cellular ATP concentration. Changes in these and other physiological parameters are continuously measured by clinicians in the treatment of any kind of brain injury, stroke, brain hemorrhage or other conditions where cerebral blood flow is compromised.

The relationship between these physiological parameters and the blood flow is complex. Fig. 3.1 shows the effect that variations in MABP, \( P_{O_2} \) and \( P_{CO_2} \) have on the cerebral blood flow. The relationships between the CBF and each one of the physiological parameters are taken from the literature [77] and shown in Table 3.3. These relationships present the percentage variation of the blood flow (\%CBF) when one of the physiological parameters is deviated from its normal value and the rest are kept constant. The total change in the cerebral blood flow (\( \Delta CBF_{\phi} \)) due to variations in the physiological parameter \( \phi_i \), is defined as

\[
\Delta CBF_{\phi} = \sum_{\phi_i} \left( \frac{\%CBF_{\phi_i} - 100}{100} \right),
\]

where \( \phi_i \) = MABP, \( P_{O_2} \), and \( P_{CO_2} \). The expressions for the functions \( \%CBF_{\phi_i} \) are shown in Table 3.3, and plotted in Fig. 3.1. Eq. 3.1 represents a linear model that
determines the variation of CBF as a result of changes in each one of the physiological parameters $\phi_i$.

When either $P_{CO_2}$ or the pH rises, or when $P_{O_2}$ in the blood falls, the CBF is increased to sweep away the wastes of cellular function, and replenish the tissue with oxygenated blood. The pH in the surrounding tissue is important because it affects neuronal activity. Low arterial oxygen tension ($P_{O_2} < 6.7$ kPa (50 mm Hg)) produces a rapid increase in CBF and CVB as seen in Fig. 3.1. A drop in the arterial $P_{O_2}$ to 18 mm Hg produces disturbances in brain function and damage to brain structural elements; and a drop in the venous $P_{O_2}$ is related to irreversible tissue damage [54]. The oxygen tension in cerebral tissue varies considerably in different areas, depending mainly in microcirculation and oxygen uptake. On the other hand, the CBF changes drastically when the arterial $P_{CO_2}$ departs from normal levels (40 mm Hg), as observed in Fig. 3.1. During hypercapnia (high $P_{CO_2}$), CBF is increased, and vice versa. Another physiological parameter measured to monitor brain function is the relation between the cerebral metabolic rate of oxygen consumption (CMRO$_2$) and CBF and temperature changes. It has been observed that CMRO$_2$ varies exponentially with temperature (Fig. 3.2a); and, at a normal body temperature, the CBF increases with the CMRO$_2$ (Fig. 3.2b). Temperature changes affect brain metabolism because temperature controls the rate at which reactions occur; thus the concentration of products and reactants becomes, between other parameters, a function of temperature. In cellular physiology, it is known that chemical gradients of substances like ions affect transport through membranes, and this alters substantially the cellular metabolic rate. Therefore, at very low or very high temperatures, the transport of some species is affected and consequently the cellular function. In particular, the transport of Na$^+$ is inhibited when temperature falls below 4°C.
### Table 3.3: Relationships between CBF and the physiological parameters [77].

<table>
<thead>
<tr>
<th>%( \text{CBF}_{\phi_i} )</th>
<th>Mathematical Expression</th>
<th>Value Range for ( \phi_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-9.3627273 + 3.8025758( MABP )</td>
<td>for ( 0 &lt; MABP &lt; 60 )</td>
<td></td>
</tr>
<tr>
<td>-6.6594872 \times 10^{-2} MABP^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+1.0904429 \times 10^{-3} MABP^3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+8.839161 \times 10^{-6} MABP^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%( \text{CBF}_{MABP} ) = 100,</td>
<td>for ( 60 \leq MABP &lt; 140 )</td>
<td></td>
</tr>
<tr>
<td>-9824.923 + 255.15379 MABP</td>
<td>for ( 140 \leq MABP &lt; 185 )</td>
<td></td>
</tr>
<tr>
<td>-2.43203203 MABP^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+1.0147878 \times 10^{-2} MABP^3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.555245 \times 10^{-5} MABP^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>241.20908 - 2.90778(P_{O_2})</td>
<td>for ( 0 &lt; P_{O_2} &lt; 40 )</td>
<td></td>
</tr>
<tr>
<td>1174.3974 - 70.115107(P_{O_2})</td>
<td>for ( 40 \leq P_{O_2} &lt; 61 )</td>
<td></td>
</tr>
<tr>
<td>%( \text{CBF}<em>{P</em>{O_2}} ) = +1.7436586(P_{O_2})^2 - 0.0194839(P_{O_2})^3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+8.232781 \times 10^{-5}(P_{O_2})^4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>104.47978 - 0.02543(P_{O_2})</td>
<td>for ( 61 \leq P_{O_2} &lt; 750 )</td>
<td></td>
</tr>
<tr>
<td>%( \text{CBF}<em>{P</em>{CO_2}} ) = 2.6(P_{CO_2})</td>
<td>for ( 0 &lt; P_{CO_2} &lt; 20 )</td>
<td></td>
</tr>
<tr>
<td>1.76562 + 2.50347(P_{CO_2})</td>
<td>for ( 20 \leq P_{CO_2} &lt; 80 )</td>
<td></td>
</tr>
<tr>
<td>158.0634 + 0.55461(P_{CO_2})</td>
<td>for ( 80 \leq P_{CO_2} &lt; 100 )</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.1: Cerebral blood flow versus the mean arterial blood pressure (MABP), the arterial partial pressure of oxygen ($P_{O_2}$), and the arterial partial pressure of carbon dioxide ($P_{CO_2}$).

Figure 3.2: a) Variation of the cerebral metabolic rate of oxygen consumption (CMRO$_2$) with the temperature, and b) Relationship between CBF versus the cerebral metabolic rate of oxygen consumption [77].
3.1.2 Intracranial Dynamics Models

In the attempt to minimize and prevent brain injury after ischemia, clinicians and anesthesiologists have studied the relations between blood flow and physiologic parameters, such as $P_{O_2}$ and $P_{CO_2}$; in this direction, several models with different degrees of complexity have been created. These models, also referred as intracranial dynamics or ICD models include the main biomechanical factors that affect the pressure $P$ and blood volume $V$ within the intracranial cavity, such as the cerebrospinal fluid dynamics, autoregulatory mechanisms, and cerebral hemodynamics. The ICD models can be broadly placed into two distinct categories, which will be referred to as black box models and physiologically based models. Physiologically based models attempt to describe cerebral autoregulation by means of differential equations which are derived from a model of the underlying physiological processes. Black box models take a data driven approach and attempt to identify the dynamic relationships of the model purely from experimental data.

Equation 3.1 shows a very simplified black box model, where the changes in the CBF due to variations in MABP, $P_{O_2}$ and $P_{CO_2}$ are added following a linear relationship. A number of more complicated mathematical models of the cerebral autoregulation exist in the literature, and have been used for clinical testing [46, 80]. In the physiological models that describe the cerebral autoregulation mechanisms, blood flow is described by considering lumped elements or compartments whose transfer characteristics are represented by first order non-linear differential equations. A collection of these elements forms a hydrodynamic circuit from which a system of coupled non-linear differential equations is derived. The hydrodynamic circuit is represented by an electrical equivalent circuit obeying the same transfer characteristics. Hydrodynamic circuits represent the relationship between flow $Q$, and pressure $P$. A hydraulic resistance $R$ requires a pressure difference $\Delta P$ to allow a flow $Q$ given by the equation

\[ Q = \frac{\Delta P}{R} \]
A hydraulic capacitance $C$ stores a volume $V$ when the fluid inside a vessel compartment is at a pressure $P$, and the blood volume $V$ is given by the relation

$$V = CP$$

From these equations, it can be seen that a hydrodynamic circuit has an electrical analogy, in which the blood flow is equivalent to the electrical current, the pressure is equivalent to the electrical voltage, and the blood volume is equivalent to electrical charge.

The ICD models are based on the constancy of the intracranial volume or the Monroe-Kellie doctrine, and divide the intracranial volume into compartments that represent arteries, capillaries, veins and the cerebrospinal fluid (CSF). Each vessel compartment has a blood volume, vessel resistance $R$ and vessel compliance $C$ associated to it. Vessel resistance and blood volume in each compartment are calculated by simulating each vessel segment as the parallel arrangement of vessels of equal radius. The blood volume in each vessel segment is proportional to the second power of the characteristic vessel radius. According to the Hagen-Poiseuille law [53], the hydraulic resistance of a vascular bed is given by

$$R = \frac{128\mu_{\text{plasma}}L}{16\pi Nr^4}, \quad (3.2)$$

where $L$ represents the characteristic length of the vascular bed, $r$ the characteristic radius of the vessels, $N$ the average number of vessels in the vascular bed, and $\mu_{\text{plasma}}$ corresponds to the plasma viscosity. The characteristic vessel radius and the compliance of a vascular bed or compartment depend on the regulatory mechanisms, oxygen concentration and $CO_2$ concentrations, which act on the smooth muscle tension of arteries.

There are two major physiology based intracranial dynamics models that introduce gas exchange and cerebral autoregulation, one proposed by Ursino et al [79], and the other by Lu et al [47]. Figure 3.3 shows the electric analog of the intracranial model proposed by Ursino et al. In this model, four compartments are distinguished
Figure 3.3: Electric analog of the intracranial dynamics model proposed by Ursino et al [80]. $G_i$, $C_i$ and $P_i$ represent the vessel conductance, compliance and intravascular pressure, respectively for the proximal ($i = 1$), and distal arteries ($i = 2$). $P_c$, $P_v$ and $P_{vs}$ correspond to the capillary, venous and venous sinus pressure. $q$ is the cerebral blood flow (CBF); $P_{vs}$ and $P_{ev}$, denote the sinus venous and central venous pressure, respectively; $P_{iv}$, represents the intracranial pressure (ICP); $C_{ic}$, intracranial compliance; $G_{pv}$ and $C_{vs}$, hydraulic conductance and compliance of large cerebral veins; $G_{vs}$, hydraulic conductance of terminal intracranial veins (bridge veins and lateral lacunae or lakes); $G_{ve}$ and $C_{ve}$, hydraulic conductance and compliance, respectively, of extracranial venous pathways; $G_f$ and $G_o$, conductances to cerebrospinal fluid (CSF) formation and CSF outflow; $q_f$ and $q_o$, rates of CSF formation and CSF outflow; and $I_t$, artificial CSF injection rate.
which correspond to: arterial, capillary, venous, and CSF. The exact mathematical
description of the this model is discussed in detail in Refs. [79, 49, 81]. In the
model of Fig. 3.3, the arterial bed is divided into large and small pial arteries, this
differentiation is important because regulatory mechanisms and oxygen absorption
mechanisms vary with the arterial radius. The model is characterized by a system of
coupled non-linear differential equations with state variables $P_{pa}, P_{tc}, P_v, V_{pa1}, x_{aut,j},$
$x_{O2,j}$ and $x_{CO2,j}$, which represent pial arterial pressure, intracranial pressure, venous
pressure, pial-arterial volume, the autoregulation control variable, the oxygen control
variable and the $CO_2$ control variable respectively. $x_{aut,j}$ is a function of the arterial
radius, autoregulatory mechanism and gas dynamics; $x_{O2,j}$ and $x_{CO2,j}$ are functions
of the gas concentration in the arterial and venous blood, the cerebral blood flow and
the tissue metabolic rate. The variation of $x_{aut,j}$ $x_{O2,j}$ and $x_{CO2,j}$ are reproduced by
means of a low pass filter, where each one is characterized by a gain factor ($G_{aut,j},$
$G_{CO2,j}, G_{O2,j}$) and a time constant ($\tau_{aut,j}, \tau_{CO2,j}, \tau_{O2,j}$) as seen in Fig. 3.4. Detailed
solution of these equations to compute CBF and all of the state variables in response
to an experimentally measured MABP is described in [82, 46].

**Temperature Effect on the Intracranial Dynamics**

Chapter 1 mentioned the importance of knowing the cerebral blood flow and metabolic
activity to determine the brain temperature, in the present chapter, the factors that
affect the cerebral blood flow as well as the mathematical models used to describe
it have been presented. On the other hand, Temperature affects autoregulation, the
coupling between cerebral blood and metabolism, the tissue oxygen delivery, and it
has been observed that temperature instabilities affect intracranial homeostasis [69].
As a result, it is important to include the effect of temperature in the cerebral dynamics
when trying to apply temperature as one of the treatment variables (hypothermic
therapies). However, none of the ICD models described in the literature incorporates
the temperature effect in the calculation of blood flow.
Figure 3.4: Block diagram describing the action of cerebrovascular regulation mechanisms, according to the model shown in this figure [81]. \( j = 1, 2 \) denotes the segments of large and small pial arteries, respectively. The upper branch represents the \( CO_2 \) mechanism, the middle branch is the oxygen-dependent mechanism, while the lower branch characterizes additional mechanisms, necessary to explain autoregulation results (pressure-dependent mechanisms in large pial arteries, and flow-dependent in small pial arteries). CPP is the cerebral perfusion pressure; CBF cerebral blood flow; \( PaCO_2 \) is the \( CO_2 \) arterial pressure; \( SoO_2 \) is the oxygen saturation in cerebral venous blood. \( G \) and \( \tau \) represent the gain and time constant of the corresponding mechanism; the symbol \( 1/\tau_s \) stands for a low-pass filter. \( ACO_2 \) is an attenuation factor on \( CO_2 \) reactivity, induced by cerebral tissue ischemia. \( M_j \) is the activation factor, which determines the level of smooth muscle contraction.
The current research uses a black box model (Eq. (3.1)) and incorporates the effect of temperature on the metabolic activity and blood flow (see Chapter 4), but the first steps towards studying the effect of temperature on the tissue oxygen delivery are presented in Appendix D, where the effect of temperature on factors such as the plasma viscosity, the oxygen affinity of blood, and the oxygen diffusion are studied. Finally, the coupling of the thermal model presented in the next chapter with and extended cardiopulmonary model [47] is important to study not only the effect of temperature in the blood flow, but in the intracranial dynamics, and that is left as future work.

3.2 Cerebral Ischemia

The central nervous system has a high metabolic rate and depends upon a continuous blood supply for nutrition and for clearance of metabolic end-products. In the event of the interruption of circulation, function quickly fails, and if circulation is not restored in a short time, irreversible damage to the neurons occurs. A drop in cerebral perfusion, can cause a critical energy crisis to the cerebral tissue. The most common causes of energy crisis are a drop of cerebral perfusion also known as ischemia and a reduction in the oxygen content of blood referred as hypoxia. Both cerebral ischemia and cerebral hypoxia can cause lasting damage or even death. However, there are significant differences in these conditions.

Cerebral hypoxia refers to a lack of oxygen to the brain, even though blood flow and pressure may be normal. It can be caused by many conditions, including: drowning; asphyxiation from smoke inhalation; strangling; birth injury; carbon monoxide poisoning; choking; compression of the trachea; general anesthesia; and diseases that paralyze the respiratory muscles. On the other hand, cerebral ischemia is a lack of blood flow to the brain due to the following causes: cerebral atherosclerosis; emboli of cardiac origin; cardiac disease leading to systemic hypotension; lacunar infarction; cerebral artery thrombosis due to nonatherosclerotic abnormalities (e.g.,
polycythemia, thrombocytosis); cerebral arterial spasm following subarachnoid hemorrhage; cerebral vasoconstriction associated with migraine; and cerebral vein and sinus thrombosis.

While ischemic changes cause hypoxia, not all hypoxia is caused by ischemic changes; ischemia causes not only energy failure but results also in accumulation of lactic acid and other toxic metabolites that are normally removed by the circulation. As a result, the hypoxia patient who survives has a better clinical prognosis than the ischemic patient who survives. This is because with hypoxia alone, blood flow is preserved. The blood flow, even hypoxic blood, helps to preserve tissue homeostasis; for example, regulation of the blood pH. Blood flow is therefore important, above and beyond the delivery of oxygen.

Ischemia is classified into global ischemia, such as as in cardiac arrest, asphyxia or hemorrhage; and focal ischemia, which occurs during stroke or embolic occlusion of one of the arteries that feeds blood to the brain. Animal experiments have shown that ischemic injury develops more rapidly on focal ischemia than on global ischemia, and in both cases, hypothermia has shown protective results and has improved the outcome [65, 31]. There are two different models of focal cerebral ischemia, which correspond to: pMCAo (permanent occlusion of the middle cerebral artery MCA) and tMCAo (temporary occlusion of the MCA). For ischemia produced by temporal vessel occlusion, mild to moderate hypothermia improves the outcome, and for the case of permanent vessel occlusion, deep hypothermia shows better protective results than moderate hypothermia. The protective effect of hypothermia during and after ischemia is attributed to the reduction in the tissue metabolic activity and the suppression of ischemia-induced inflammatory reactions that increase the infarct size. It has been observed that timing as well as duration are important factors affecting the success of hypothermic therapies [32, 65, 31]. In addition, rapid or uncontrolled rewarming after hypothermia may have adverse effects which may negate the benefits of cooling. As a result, analysis of cooling onset and cooling rate using a thermal model
that incorporates physiological variations of blood flow and metabolic activity during ischemia and post ischemia are useful in the study of hypothermic therapies applied to focal cerebral ischemia produced by traumatic brain injury (TBI), subarachnoid hemorrhage (SH) or stroke.

Given the important effect that hypothermia has in the outcome of hypoxia-ischemia, this study uses a thermal model to determine the temperature variations in the brain tissue during global and regional ischemia, and variations in physiological parameters that affect the cerebral blood flow. The objective of this study is to determine the tissue temperature variation during hypoxia, circulatory arrest, and stroke, and to analyze the effect of systemic and localized hypothermia during such conditions.

3.2.1 Effect of Temperature on Ischemic Brain Injury

Treatment of hypoxia-ischemia produced by asphyxia is very important due to its occurrence in newborns during delivery. On the other hand, hypoxia-ischemia produced by stroke or circulatory arrest is one of the most common factors producing neurological problems in adults. Over the past 15 years, it has been recognized that brain temperature influences the extent and evolution of brain injury after hypoxia-ischemia [37]. In has been observed that hypothermia reduces the extent of brain injury and improves patient outcome, and that febrile episodes after or during ischemia worsens the possibility of recovery.

Hypoxia-ischemia triggers a cascade of events characterized by reduction in CBF and oxygen substrates. This phase is referred as primary energy failure, and it is associated to the following mechanisms: reduction in high energy compounds, loss of membrane ionic homeostasis, unbalance of excitatory neurotransmitters, increase in intracellular calcium and inhibition in protein synthesis. Primary energy failure is followed by the secondary energy failure stage, where acute energy depletion and total cell death is observed. The severity of secondary energy failure depends on the
extent of energy depletion observed in the primary stage. The time interval between primary and secondary energy failure is thought to be a latent phase where therapies to reduce brain damage can still be applied, this time is also referred as *therapeutic window*. As mentioned before, several experiments [35, 37, 16, 34, 7, 55, 84] have shown that hypothermia in adults and newborns help to reduce the extent of brain injury following hypoxia-ischemia by: reducing the blood flow and energy utilization rate of the tissue, blunting the release of excitatory neurotransmitters associated with ischemia (glutamate); and reducing the free radical induced injury.

Because of the effect of temperature in the evolution of the primary and secondary energy failure stages, and the occurrence of conditions that produce hypoxia-ischemia, the knowledge of brain temperature as well as temperature control techniques are very important in improving the outcome of patients after asphyxia, stroke or circulatory arrest. The previous argument together with the fact that brain temperature measurement is highly destructive justify the application of thermal models that incorporate the cerebral blood flow and metabolism in the study of hypoxia-ischemia produced by asphyxia, circulatory arrest or stroke, as well as hypothermic therapies applicable to improve patient outcome. Next chapter shows the thermal model that will be employed in the present study, and describes the brain temperature calculations performed presented in Chapters 5, 6 and 7.
Chapter 4

Thermal Model

4.1 General Model Description

The thermal model used in the present study consists in a bioheat type equation that incorporates temperature dependent metabolic heat generation and blood flow, and has the following form

\[
\rho C_p \left( \frac{\partial T}{\partial t} \right) = \nabla \cdot (k \nabla T) + \rho_b c_b W_b(T) (T_a - T) + q_m(T),
\]

(4.1)

where \( T \) and \( T_a \) correspond to the tissue and arterial temperature, respectively; \( W_b \) represents the tissue blood perfusion, and \( q_m \) denotes the metabolic heat generated by the tissue. \( W_b \) and \( q_m \) are functions of temperature and physiological parameters as discussed in previous works [40, 41], and vary with time during ischemia or for the different cooling strategies, as it will be discussed latter. The parameters \( \rho \), \( C_p \), and \( k \) represent the density, heat capacity and thermal conductivity, and are considered constant within each tissue. \( \rho_b \) and \( c_b \) represent the density and heat capacity of blood.

The metabolic heat \( q_m \) corresponds to the heat released as a result of the chemical reactions taking place at the tissue, and it is approximated by

\[
q_m = \epsilon MRO_2(T),
\]

(4.2)

where \( MRO_2 \) is the tissue metabolic rate of oxygen consumption, and \( \epsilon \) is a constant that represents the amount of heat generated during the aerobic glucose metabolism, and has a value between 4.5 - 5.01 cal/ml \( O_2 \). Experiments [73] show that, the \( MRO_2 \) increases exponentially with the temperature following the \( Q_{10} \) law

\[
MRO_2(T) = (MRO_2)_0 Q_{10}^{\frac{T-T_a}{10}},
\]

(4.3)
Table 4.1: Physical and physiological parameters for the head model

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Bone</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_i$ (W/m°C)</td>
<td>0.50</td>
<td>0.410</td>
<td>0.34</td>
</tr>
<tr>
<td>$\rho_i$ (kg/m$^3$)</td>
<td>1050</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>$c_i$ (J/kg°C)</td>
<td>3700</td>
<td>2300</td>
<td>4000</td>
</tr>
</tbody>
</table>

For the blood, $c_b = 3800$ J/Kg°C, and $\rho_b = 1050$ Kg/m$^3$

where $(MRO_2)_o$ is the metabolic rate of oxygen consumption at the normal average arterial temperature $T_a$. Combining Eqs. (4.2) and (4.3), the tissue metabolic heat can be expressed as

$$q_m = q_o Q_{10}^{(T - T_a)/10}, \quad (4.4)$$

where $q_o = \epsilon(MRO_2)_o$ is the basal metabolic heat released by the tissue.

Experimental results [24, 73], suggest that a significant correlation exists between the cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen consumption ($CMRO_2$). It has been observed that these parameters are linearly related [77]; the proportionality between the $CMRO_2$ and the cerebral blood flow is explained as a result of regulatory mechanisms that increase blood flow to sustain cerebral function. From this observation, it is assumed that the blood perfusion for the brain tissue can be expressed following the $Q_{10}$ law of Eq. (4.3)

$$W_b(T) = W_b^o Q_{10}^{(T - T_a)/10}, \quad (4.5)$$

where $W_b^o$ is the tissue blood perfusion at the normal average arterial temperature $T_a$, and this is a function of physiological parameters such as mean arterial blood pressure (MABP), concentrations of oxygen and $CO_2$ in the arterial blood and the metabolic activity of the tissue [40].

Equation (4.1) can be solved using either a convective boundary condition at the skin surface or for the case of fixed temperature at the skin surface as indicated by
Eqs. 4.6a and 4.6b, respectively.

\[
(k\nabla T) \cdot \hat{n}_S = h(T_\infty - T), \\
T|_S = T_{skin},
\]

(4.6a) (4.6b)

where \(k\) is the thermal conductivity, \(\hat{n}\) is normal to the skin surface \(S\), \(h\) is the convection coefficient, \(T_\infty\) is the temperature of the surrounding air, and \(T_{skin}\) is the temperature of the skin. Determination of the convection coefficient \(h\) is a complicated process that requires boundary layer theory or measurements involving sublimation of naphthalene [28]. The convection coefficient is calculated by approximating the body by a series of cylinders of different sizes. Convective heat loss due to natural or forced convection occurs because of the temperature difference between air and skin. In the case of natural convection, the air next to and touching the body surface becomes heated by conduction and raises as it becomes less dense, generating an upward moving envelope of warm air. For a standing naked subject, the average skin temperature is about 33°C, the natural convective boundary layer has a thickness of 180 mm at the level of the face, and the maximum velocity of air at this height is about 0.5 m/s and occurs about 20 mm away from the skin surface [14]. For the case of natural convection, the average convection coefficient is about \(h = 5 \text{ W/m}^2\text{°C}\) [28]. It is important to mention that postural changes produce large differences in flow patterns and heat losses around the skin as seen in Fig. 4.1.

For the case of forced convection, the heat loss pattern over the human body is similar to that of a heated cylinder in a moving air stream, as shown in Fig. 4.2. This figure shows the local convective heat loss coefficient at the middle plane of a bald subject; the air velocities range between 0.15 and 1.4 m/s. For the highest speed the occurs at the front and the lowest where the flow breaks away from the skin surface at the top of the head. Several measurements [14] have shown that the convection coefficient \(h\) is proportional to \(\sqrt{U}\). The average convection coefficient \(h\) for the case of forced convection used in this calculation is set equal to 30 \(\text{W/m}^2\text{°C}\), which corresponds to the average value of \(h\) for a subject running at a mean speed of
4.5 m/s.

4.2 Layered Head Model

The head is mathematically approximated as a layered hemisphere; for the calculations three different layers are considered, which correspond to skin, bone, and brain tissue, as shown in Fig. 4.3. To determine the time dependent temperature distribution in the head, the following bioheat equation is used

\[
\frac{\rho C_p}{k} \left( \frac{\partial T}{\partial t} \right) = \frac{\partial^2 T}{\partial r^2} + \frac{2}{r} \frac{\partial T}{\partial r} + \frac{1}{r^2 \sin \theta} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial T}{\partial \theta} \right) + \frac{\rho_b c_b}{k} W_b (T_a - T) + \frac{q_m}{k},
\]

where the radial coordinate \( r \) extends from \( r = 0 \) at the center of the head to \( r = R \) at the skin surface, and the angle \( \theta \) extends from \(-\pi/2\) to \( \pi/2 \). In (4.1). \( T \) corresponds to the tissue temperature, \( W_b \) represents the blood perfusion term, and \( q_m \) denotes the metabolic heat generated by the tissue. The parameters \( \rho, C_p, \) and \( k \) represent the density, heat capacity and thermal conductivity, and are considered constant within
Figure 4.2: Local convective heat loss coefficient $h$ ($W/m^2°C$), on the head of a bald subject in forced convection with air velocities ranging between 0.15 and 1.4 m/s. The highest heat loss occurs at the front leading surfaces and the lowest is at the top of the head where the flow breaks away [14].

Each layer. Finally, $\rho_b$ and $c_b$ correspond to the density and heat capacity of the blood.

In this model, $W_b$ and $q_m$ are assumed functions of the temperature as described before in equations (4.5)-(4.4). Consideration of these functional relations in a thermal model is important when trying to study stress conditions like ischemia or hypothermia because the metabolic activity $q_m$, and the organ blood flow $W_b$ vary considerably during sickness, trauma or under the effect of drugs, such as anesthetics.

The numerical values for the specific heat of blood and the other tissue layers, as well as the tissue density ($\rho_t$) and the thicknesses ($r_t$) were assumed equal in magnitude to those reported in Ref. [95], and are presented in Table 2.1. Variations in the magnitude of the tissue heat capacities were observed in the literature, but these variations had little effect in the calculations. The thermal conductivity values $k_t$ given in Table 2.1 were found in a compilation of tissue thermal conductivity values
of different species and tissues[27].

To solve (4.1), the following boundary conditions are introduced at the skin surface ($r = R$)

\begin{align}
  \left. k \frac{\partial T(r, \theta, t)}{\partial r} \right|_{r=R} &= h (T_\infty - T(r, \theta, t)), \\
  \left. \frac{\partial T(r, \theta, t)}{\partial r} \right|_{\theta=\pm \pi/2} &= 0, \\
  T(r, \theta, t)|_{t=0} &= f(r, \theta),
\end{align}

where $h$ represents the heat convection coefficient, and $T_\infty$ denotes the external air temperature. Equation (4.8a) represents the forced convection condition at the skin surface, Eqn. (4.8b) denotes an insulated boundary condition at the base of the brain ($\theta = \pm \pi/2$), and Eqn. 4.8c corresponds to the initial temperature distribution.

Because the tissue thermal properties vary from layer to layer, and are assumed constant within each layer, continuity of the temperature and the heat flux on the layer interfaces are required at the layer interfaces.

\begin{align}
  T_i(r, \theta, t)|_{r=r_i} &= T_{i+1}(r, \theta, t)|_{r=r_i}, \quad \text{for } i = 1, \ldots, M - 1 \quad (4.9a) \\
  k_i \left. \frac{\partial T_i(r, \theta, t)}{\partial r} \right|_{r=r_i} &= k_{i+1} \left. \frac{\partial T_{i+1}(r, \theta, t)}{\partial r} \right|_{r=r_i}, \quad \text{for } i = 1, \ldots, M - 1, \quad (4.9b)
\end{align}
where the subindex $i$ represents the $i$th layer indicated in Fig. 4.3, $M$ is the number of layers considered in the system ($M=3$), and $r_i$ the radial position of the $i$th layer interface.

Assuming a thermal and geometrical symmetry about the $y$ axis (Fig. 4.3), and taking the physical parameters $\rho$, $C_p$, and $k$, as well as the temperature distribution independent of the angle $\theta$, the governing equation (4.1), the boundary conditions given in (4.8a- 4.8b), and the initial condition (4.8c) are reduced to the following one dimensional time dependent system of equations:

$$
\frac{\rho C_p}{k} \left( \frac{\partial T}{\partial t} \right) = \frac{d^2 T}{dr^2} + \frac{2}{r} \frac{dT}{dr} + \frac{\rho \phi c_b}{k} W_o (T_a - T) + \frac{q_m}{k},
$$

$$
\left. k \frac{\partial T}{\partial r} \right|_{r=R} = h (T_\infty - T),
$$

$$
\left. \frac{\partial T}{\partial r} \right|_{r=0} = 0,
$$

$$
T(r,t)|_{t=0} = T_o(r),
$$

where $T_o$ corresponds to the steady state temperature distribution.

The system of equations (4.10) together with the corresponding continuity of temperature and heat flux at the layer interfaces are solved using a finite differences formulation. Since $W_b$ and $q_m$ are functions of the temperature $T$, we apply an iterative method to solve the nonlinear system of equations [61].

### 4.3 Realistic Head & Neck Model

In the present study, Eq. (4.1) is solved in a three dimensional model of the head and neck obtained from a CT tomography scan of an adult male. For the calculations three different tissue types are considered, which correspond to skin or muscle, bone and brain tissue. The tissue thermophysical properties for each one of the tissues considered in the calculations are shown in Table 4.1. Fig. 4.5 shows the surface mesh generated after tissue identification and segmentation. The mesh used is a non structured tetrahedral mesh composed by 5233 nodes and 27400 tetrahedra. To
obtain the realistic geometry of the head and use our thermal model to determine the temperature distribution in this system, the following steps were followed:

- Get the tomographic scan
- Perform the segmentation or tissue classification (bone/brain/muscle/skin)
- Use the results from the segmentation to create a surface reconstruction (Fig. 4.5), by employing the marching cubes algorithm.
- Use the reconstructed surface to create a FE mesh
- Include the generated mesh into a commercial FE solver with the corresponding material properties and boundary conditions and run the required simulations.

These steps are exemplified in the diagram shown in Fig. 4.4. The tissue segmentation can be done using several commercial software packages, and the surface reconstruction is performed using a well known algorithm called Marching Cubes. Using the reconstructed surface, a FE mesh can be created with a grid generator and the results can be imported to a FE solver, such as ABAQUS/Standard. To complete the steps described previously, the software Amira 3.0 by Amiravis was used. Amira is the most complete package for segmentation and FE mesh generation in the market.
Figure 4.5: Surface mesh generated from a CT scan considering 3 different tissues: skin, bone and brain.

Given the temperature dependence of $W_b$ and $q_m$, Eq. (4.1) is a non-linear equation which is solved using ABAQUS/STANDARD and an external user defined subroutine to introduce the temperature dependent heat generation due to the volumetric blood perfusion and tissue heat production. As shown in Fig. 4.6, the system is solved considering that the neck base is insulated, and the skin surface subjected to either natural convection, forced convection or fixed temperature, depending on the cooling condition to be studied.

4.4 General Description of the Calculations Performed

As mentioned in Chapter 3, the knowledge of brain temperature is important in the treatment of cerebral ischemia, and the application of hypothermia in such conditions improves the patient outcome. Based on this idea, this study uses a thermal model to study the application of different hypothermic therapies to the case of global ischemia produced by circulatory arrest or asphyxia, and of focal ischemia produced by stroke.

This study first started with the simplified 3-layer model to introduce the effect of physiology and boundary conditions on the brain temperature distribution. Also
using the simplified geometry, the temperature variation due to global ischemia and different cooling strategies were considered. As the next step, direct brain temperature measurements performed in swine were used to validate the thermal model. Finally, after observing the importance of the geometry and accurate thermophysical properties, a realistic model (Section 4.3) was used to study cooling conditions during global and local ischemia.

In the next paragraphs the calculations presented in the following chapters are summarized. The results are divided in two major groups that correspond to the calculations using the layered model described in Section 4.2, and the calculations using the realistic geometry model of Section 4.3.

- **Effect of external boundary conditions and physiology.** In this case, the steady state temperature gradients within the different tissue layers are analyzed for different external boundary conditions and values of the physiological parameters (MABP, PaCO₂, and PaO₂) that affect the cerebral blood flow. Cooling is achieved either by conduction or external convection at the skin surface, and the energy equation is solved for a geometrically simplified or layered
model are presented. The results obtained for this study were published in Refs. [40] and [41]; and are included in Section 5.1

- **Brain temperature during hypothermic circulatory arrest.** This study analyzes the effect of different cooling and rewarming strategies on the brain temperature distribution before and after circulatory arrest in adults and children. These results are shown in Section 5.2 and Ref. [43]. The temperature variations during systemic cooling, circulatory arrest, and rewarming are calculated using a layered thermal model that incorporates physiological parameters and variations in blood flow and metabolic activity during circulatory arrest. The calculations presented here explain why sometimes hypothermia does not show the expected neuroprotective effect.

- **Model Validation using data for swine.** Chapter 6 presents the numerical simulations performed to analyze the brain temperature reduction in swine during selective head cooling, whole body cooling or while the animals experience global ischemia. Brain temperature is calculated using a time dependent layered thermal model that incorporates available experimental measurements of the rectal temperature, the cerebral blood flow and the cerebral metabolic rate of oxygen consumption. The calculated temperature distribution is validated against the in-vivo temperature measurements recorded during the different experiments. These results were published [45].

- **Temperature calculations during global ischemia.** Calculations of temperature distribution during selective head cooling, whole body cooling, cardiopulmonary bypass, and circulatory arrest are presented for the realistic head and neck geometry obtained from a CT scan of an adult male. The transient temperature distribution is calculated during different cooling strategies and variations in cerebral blood flow. The results of this study are presented in Section 7.1 and published in [44].
• Brain temperature calculation during stroke and various cooling modalities These calculations are shown in Section 7.2, and show the temperature variations in the human brain due to focal or regional ischemia produced by stroke, as well as the effect of surface and whole body cooling during and after stroke onset. The thermal model used introduces temporal measurements of regional cerebral blood flow and metabolic activity, and the realistic three-dimensional geometry of the head and neck of Section 4.3. The results of this study can be used to analyze the transient temperature in the healthy brain tissue and the infarct region during and after vascular occlusion to improve the application of hypothermia in the treatment of stroke and focal ischemia.
Chapter 5

Calculations using the Layered Thermal Model

5.1 Effect of External Boundary Conditions and Physiology

This section presents calculations of the changes in the brain temperature as a result of surface cooling and variations in the physiological parameters that affect and control the cerebral blood flow as described in Chapter 3. The calculations were obtained using the 3-layer thermal model described in the previous chapter and Refs. [40, 41]. The thermal model introduces a temperature dependent tissue metabolic heat generation and blood flow, as well as regulatory mechanisms of the cerebral blood flow. The consideration of physiological parameters in a thermal model is important given the effect that blood flow has on tissue temperature and because it gives information about how specific conditions, such as brain edema, hypoxia, hypercapnia, or hypotension, affect the temperature distribution within the brain. Also, the study of different surface cooling strategies give us information on how to improve hypothermic therapies used in medical practice. Our work, on a layered head model, shows that variations of the physiological parameters have profound effect on the temperature gradients within the head.

In the calculations, the metabolic heat generation $q_m$ and the tissue blood perfusion $W_b$ for the skin and bone layer are assumed constant, and equal in magnitude to the values given in Table 5.1. For the brain tissue region, $W_b$ and $q_m$ are function of the temperature and metabolism as shown in Eqs. (4.5)-(4.4), respectively. The relations between the cerebral blood perfusion $W_b$ and the physiological parameters are obtained from a cerebral regulation model [77], and are incorporated as follows

$$W_b(\phi, T, r) = W_o (1 + \Delta CBF_\phi), \quad (5.1)$$
Table 5.1: Physical and physiological parameters for the 3-layer head model

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Skull</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_i$ ($W/m^\circ C$)</td>
<td>0.50</td>
<td>1.16</td>
<td>0.34</td>
</tr>
<tr>
<td>$\rho_i$ ($kg/m^3$)</td>
<td>1050</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>$c_i$ ($J/kg^\circ C$)</td>
<td>3700</td>
<td>2300</td>
<td>4000</td>
</tr>
<tr>
<td>$W_o$ (ml/min 100 grs of tissue)</td>
<td>50.02</td>
<td>0.1</td>
<td>2.0</td>
</tr>
<tr>
<td>$q_o$ ($W/m^3$)</td>
<td>10437</td>
<td>368.3</td>
<td>363.4</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>85</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

For the blood, $c_b = 3800 \ J/Kg^\circ C$, and $\rho_b = 1050 \ Kg/m^3$

where $W_o$ is the average blood perfusion in the cerebral tissue at normal core temperature; $\Delta CBF_\phi$ represents the percentile change in the cerebral blood flow due to variations in the physiological parameter $\phi_i$, which is defined as

$$\Delta CBF_\phi = \sum_{\phi_i} \left( \frac{\%CBF_{\phi_i} - 100}{100} \right),$$

(5.2)

where $\phi_i = MABP, PaO_2, PaCO_2$, and $CMRO_2(T)$). The expressions for the functions $\%CBF_{\phi_i}$ are documented in the literature [77], and plotted in Fig. 3.1.

The exponential model for $q(T)$ was known by physiologists since 1944 [73]; however, it has been considered only recently by Zhu et al [95] in a thermal model of the head. This work includes not only the temperature dependent metabolic heat described in Eq. 4.4, but introduces for the first time the effect that some physiological parameters have on the organ blood flow and the tissue temperature distribution by using organ regulatory models.

5.1.1 Varying the Boundary Condition at the Skin

To analyze the effect of variations in the heat transfer coefficient $h$, we keep the surrounding air temperature $T_{air}$ constant, and calculate the radial temperature dis-
tribution for $h = 25$, $50$, $75$, and $100 \text{ W/m}^2\text{°C}$, as well as the case of fixed temperature at the external skin surface ($h \to \infty$) [40] (see Fig. 5.1). For these calculations, the normal average values of the physiological parameters were considered, that correspond to MABP=100 mmHg, $PaCO_2 = 40$ mmHg, and $PaO_2 = 100$ mmHg.

To study how variations in the surrounding air temperature $T_{\text{air}}$, affect the radial temperature distribution within the head, we keep $h$ constant, and set $T_{\text{air}}$ equal to 5, 10, and 20 °C, as shown in Fig. 5.2; and as before, we use the normal average values of the physiological parameters. The values of $h$ and $T_{\text{air}}$ chosen for these calculations are based on other studies involving head cooling by external convection [59], and in the fact that the room temperature in an operating or emergency room is below 20 °C. From [59], the value of $h = 4 \text{ W/m}^2\text{°C}$ represents convection to still air, and using the Whitaker relation for the average heat transfer coefficient for flow across a single sphere [5], the air velocity corresponding to $h = 25 \text{ W/m}^2\text{°C}$ is of approximately 25 m/s.

In the figures presented in this section, the temperature distribution in the deep structures of the head (gray and white matter) varies within a distance $d$ (*penetration depth*) from the interface between the brain and skull. The temperature distribution in the deeper structures of the head, tends to a limiting value close in magnitude to the arterial temperature $T_a$. This limiting temperature is reached as a result of the large volume of warm arterial blood continuously perfusing the brain tissue. The high blood perfusion in the brain tissue, makes it very difficult to alter the deep brain temperature, and reduces the effect of the external boundary conditions of either convection cooling or the contact cooling ($h \to \infty$).

The penetration depth $d$, increases in magnitude with the convection coefficient $h$, until it reaches a maximum constant value that depends on the surrounding air temperature. For $T_{\text{air}} = 10°C$, the penetration depth varies from 4.6 cm when $h = 4 \text{ W/m}^2°\text{C}$ to 6.2 cm for $h \to \infty$. On the other hand, $d$ decreases linearly as the external air temperature raises, and the slope associated depends on the value of $h$. 
Figure 5.1: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Arterial temperature \( T_a = 37^\circ C \), external air temperature \( T_{air} = 10^\circ C \), and heat transfer coefficient \( h = 25, 50, 75 \) and 100\( W/m^2 ^\circ C \). The last solid curve, represents the limit of \( h \rightarrow \infty \), and agrees with the results presented in [40] for constant surface temperature.
Figure 5.2: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Heat transfer coefficient $h = 75 \text{W/m}^2\text{C}$, arterial temperature $T_a = 37^\circ\text{C}$, and external air temperature $T_{air} = 5, 10$ and $20^\circ\text{C}$.

In Figs. 5.1 and 5.2, we note that the temperature at the skin surface is a function of $T_{air}$ and $h$. We observe that the temperature at the external skin surface decreases exponentially as the heat transfer coefficient $h$ increases, and varies proportionally to the air temperature $T_{air}$. We will show latter that the temperature at the skin surface also changes with the physiological parameters, but this change is small.

5.1.2 Varying the Physiological Parameters

We are interested in the variations between the normal temperature distribution, and the temperature distributions obtained when the physiological parameters depart from their normal average values. To analyze these variations, we vary one of the physiological parameters at a time, keeping the others in their average normal values ($MABP=100 \text{ mmHg}$, $PaO_2=100 \text{ mmHg}$, $PaCO_2=40 \text{ mmHg}$), and we monitor the penetration depth $d$, the external skin temperature, and the maximum temperature difference between the normal average temperature distribution and the temperature
Figure 5.3: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Arterial temperature $T_a = 37^\circ C$, external air temperature $T_{air} = 10^\circ C$, $PaCO_2 = 40$ mmHg, $PaO_2 = 100$ mmHg, mean arterial blood pressure $MABP = 45, 100, 160$ mmHg, and heat transfer coefficient $h = 25$ and $75 \, W/m^2^\circ C$. The last set of curves, corresponds to the limit of $h \to \infty$, and agrees with the results presented in [40] for constant surface temperature $T_o = 10^\circ C$.

distribution produced by values of the physiological parameter different from the normal average.

In Figs. 5.3-5.5, we vary the physiological parameters and the heat transfer coefficient $h$. We consider the cases of $h = 25 \, W/m^2^\circ C, 75 \, W/m^2^\circ C$, and the particular case of $h \to \infty$, which reduces the temperature distribution obtained for the case of fixed external surface temperature $T_o = T_{air}$ [40]. In these plots we observe that, regardless of the numerical value of the physiological parameters, as the heat transfer coefficient increases, the penetration depth increases, and reaches its maximum when for $h \to \infty$. This indicates that contact cooling is the best way to reduce the tissue temperature.

In Fig. 5.3, we show how variations of the MABP affect the temperature distribution. Changes in the $MABP$ are produced by drugs or conditions like brain edema,
brain swelling, vessel collapse, the presence of aneurysms among others. We consider values of the MABP that correspond to mild hypotension (MABP= 45 mmHg), normotension (MABP=100 mmHg), and mild hypertension (MABP= 160 mmHg), and maintain the rest of the physiological parameters in their average normal values. Varying the MABP, the difference of temperature at the skin surface changes up to 1%, this difference reduces as the heat transfer coefficient increases. In the low pressure case, the blood flow decreases approximately 10%, producing a temperature drop that increases in magnitude with $h$. This is evidence that the external cooling has a stronger effect when the cerebral blood flow is reduced. When the MABP=160 mmHg, the CBF increases 13%, and the temperature in the bone layer and the outer part of the brain tissue increases. The maximum temperature difference between the normal arterial pressure case, and the hypotensive and hypertensive cases occurs at the Bone/Brain interface, and it is about the same magnitude in both cases because the change in the CFB is similar in both cases, and increases with the convection coefficient ($h$). The penetration depth ($d$) varies inversely with the MABP, and remains constant for mean arterial blood pressures between 50 and 140 mmHg. This variation is the result of the increase in blood flow for values of MABP lower than 50 mmHg, and the reduction in blood flow for $MABP > 140$ mmHg, as seen in Fig. 3.1.

Figs. 5.4 and 5.5, show the variation of the radial temperature distribution for different values of $PaO_2$ and $PaCO_2$, respectively, keeping the other physiological parameters in their average values and using the exponential temperature dependence for the $CMRO_2$ (Eqn. 4.3) and the metabolic heat $q_m$ (Eqn. 4.4). Variations of $PaO_2$ and $PaCO_2$ are clinically achieved by respiration of air with different concentrations of either $O_2$ or $CO_2$, or pathologically produced by asphyxiation or $CO_2$ poisoning, respectively. Figure 5.4, shows the radial temperature distribution for $PaO_2= 25, 50, 100$ and 250 mmHg. Values of the partial pressure of oxygen of less than 100 mmHg represent an hypoxic condition, and produce a CBF increase. For $PaO_2= 25$ and
Figure 5.4: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Arterial temperature $T_a = 37^\circ C$, external air temperature $T_{air} = 10^\circ C$, $PaCO_2= 40$ mmHg, $MABP= 100$ mmHg, partial pressure of oxygen $PaO_2= 25, 50, 100, 250$ mmHg, and heat transfer coefficient $h = 25$ and $75$ W/m$^2$ °C. The last set of curves, corresponds to the limit of $h \to \infty$, and agrees with the results presented in [40] for constant surface temperature $T_o=10$ °C.
50 mmHg, the CBF increases 70% and 7%, respectively; while $PaO_2 = 250$ mmHg reduces the CBF only 2% of its average value, producing a condition called hyperoxia.

Varying $PaO_2$ in the range 25-250 mmHg, the temperature difference reaches its maxima at the Bone/Brain interface, and produces a maximum local temperature change of about $1^\circ C$ and $5.4^\circ C$, for $h = 25 \frac{W}{m^2^\circ C}$ and $h \to \infty$, respectively. When $PaO_2=25$ mmHg, the penetration depth $d$ is reduced between 20 and 23 % for $h = 25 \frac{W}{m^2^\circ C}$ and $h \to \infty$, respectively. We observe that, for values of $h$ between $4 \frac{W}{m^2^\circ C}$ and $h \to \infty$, the penetration depth $d$ increases with the oxygen concentration until it reaches a maximum value. Also, as noted before, $d$ increases with the heat transfer coefficient $h$. In Fig. 5.4, we observe that for all values of $T_{air}$ and $h$ considered, the external skin temperature changes less than 4% with respect to the skin temperature value at average $PaO_2$. The increment in the penetration depth with the oxygen saturation ($PaO_2$) is the result of the reduction in the blood flow as the oxygen concentration approaches to normal values (Fig. 3.1). As $PaO_2$ increases, the volume of warm blood entering the brain tissue decreases, and the external boundary condition has more effect over the tissue temperature.

Fig. 5.5, shows the radial temperature distribution for normal concentrations of $CO_2$ ($PaCO_2=40$ mmHg) and compares it with the case of mild and severe hypercapnia, corresponding to $PaCO_2$ values of 60 and 90 mmHg. $PaCO_2$ is a strong vasodilator of the cerebral vasculature; which means that, as the $CO_2$ concentration increases, the radius of the arterioles will grow and as a result the volume of blood entering the tissue will increase (Fig. 3.1b). Hypocapnia ($PaCO_2 < 40$ mmHg), on the other hand, reduces CBF and improves the cerebral autoregulatory capacity [62], that is, it helps the brain vessels to reduce its diameter and regain elasticity after hypertension or conditions that affect the amount of blood entering the brain, like a migraine headache.

During severe hypercapnia ($PaCO_2 = 90$ mmHg), the CBF is increased over 200%. The maximum temperature difference increases with $PaCO_2$ and $h$. The
Figure 5.5: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Arterial temperature $T_a = 37^\circ C$, external air temperature $T_{air} = 10^\circ C$, $PaO_2 = 100$ mmHg, $MABP = 100$ mmHg, partial pressure of carbon dioxide $PaCO_2 = 40$, 60 and 90 mmHg, and heat transfer coefficient $h = 25$ and 75 $W/m^2\circ C$. The last set of curves, corresponds to the limit of $h \to \infty$, and agrees with the results presented in [40] for constant surface temperature $T_o = 10^\circ C$. 
penetration depth $d$ reduces as $PaCO_2$ increases, and for the values of $h$ and $T_{air}$ considered in the calculation, the penetration depth is reduced approximately 23 % with respect to the temperature value obtained for the average $CO_2$ concentration. The reduction of $d$ as the $CO_2$ tension increases, occurs as a result of the increment in the volume of warm blood entering the brain tissue. At the external skin surface, the temperature changes up to 5.33 % with respect to the value reached when $PaCO_2=40$ mmHg.

In Figs. 5.3-5.4 we observed that, when the physiological parameters depart from their normal average value, the temperature at the skin surface varies a few degrees, and the maximum temperature difference also varies. We also concluded that the penetration depth $d$ is affected by variations in the physiological parameters, changes in the air temperature and by the heat transfer coefficient $h$. We noticed that the effect of the the external boundary condition over the deep tissue temperature increases when the blood flow is reduced.

From Figs. 5.3-5.4, we observe that the penetration depth $d$ is small despite severe variations of the different physiological parameters. This is due to the high blood perfusion of the brain tissue, and the fact that this blood enters the tissue at a high temperature ($T_a$). Therefore, as one can see in Fig. 5.6, if the temperature of the deep tissue is to be altered, the arterial blood temperature $T_a$ must be changed. Variation of the arterial blood temperature is usually done through extracorporeal perfusion. As seen experimentally [62], using extracorporeal perfusion to cool the arterial blood and the help of the alterations in blood flow by the different physiological parameters can help to achieve cooling of the deep brain tissue.

5.1.3 Summary of Results

In summary, this work provides an extension to current thermal models, it introduces organ specific regulatory effects and energy utilization by considering parameters that affect tissue metabolism and organ blood flow. It is observed that any change in
Figure 5.6: Temperature distribution for a 3-layer sphere (skin/skull/brain) subject to external convection at the skin surface. Heat transfer coefficient \( h = 75 \text{W/m}^2\text{oC} \), external air temperature \( T_{air} = 10\text{oC} \), normal values of the physiological parameters, and \( T_a=35 \), and \( 37 \text{oC} \).

the cerebral blood volume, produced as a result of the regulatory mechanisms, will affect the head temperature distribution. It is observed that varying the different physiological parameters so that the CBF is increased, the temperature gradient in the external structures and the penetration depth \( d \) are reduced. However, the ability to control the deep tissue temperature of a patient strongly depends on the temperature of the arterial blood entering the brain and the external boundary conditions applied to the head surface.

5.2 Brain Temperature during Deep Hypothermic Circulatory Arrest

In this section, the effect of different cooling and rewarming strategies on the brain temperature distribution before and after circulatory arrest in adults and children is
analyzed. The temperature variations during systemic cooling, circulatory arrest, and re-warming are calculated using the 3-layer thermal model described before in Section 4.2. The results presented here incorporate previous experimental observations [1, 23, 24] regarding the duration of systemic cooling using CPB, and variations of blood flow and metabolism.

Early experience with deep hypothermia suggested that esophageal temperatures lower than 10°C caused dramatic increase in neurologic and pulmonary injury. As a result, most institutions limited systemic hypothermia to temperatures of 18°C. In the calculations presented here, the temperature distribution in the head is calculated during deep hypothermic circulatory arrest (DHCA) at 18°C. In the calculations, four stages are distinguished: the determination of the baseline temperature distribution; systemic hypothermia using CPB; circulatory arrest (DHCA); and reperfusion and re-warming. A description of these stages is presented next, and a summary can be found at Table 5.2.

For the baseline stage, the steady state temperature distribution is calculated using an arterial temperature of 37°C, the blood flow and metabolic heat values given in Table 5.3, and a mean arterial blood pressure MABP of 70 and 60 mmHg for adults and children, respectively. These calculations are performed for fixed skin temperature, and external convection.

The systemic cooling stage is divided into two parts. During the first part the arterial temperature is reduced linearly from its normal value \(T_a^o\) to \(T_{a, cool}^o\) 18°C in a time interval \(t_{cool}\) of 20, 30, and 40 minutes. In this part, the cooling rate \(m\) is defined as

\[
m = \frac{T_a^o - T_{a, cool}^o}{t_{cool}}. \tag{5.3}
\]

The second part of this stage consists in an equilibration time \(t_e\) of up to 30 minutes where the arterial temperature is kept at 18°C.

During the circulatory arrest or DHCA, the circulation is stopped at a time \(t_{CA}\) defined as \(t_{CA} = t_{cool} + t_e\), where \(t_{cool}\) and \(t_e\) correspond to the cooling and equilibration
### Table 5.2: Stages in the Computer Simulation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline temperature</strong></td>
<td>The steady state temperature distribution is calculated for the chosen boundary conditions</td>
</tr>
</tbody>
</table>
| **Systemic Cooling** | 1) Cooling arterial blood through CPB from $T_a^o = 37^\circ C$ to $T_a^{cool} = 18^\circ C$ in a time $t_{cool}$.  
2) Equilibration period, where $T_a$ is kept at $T_a^{cool} = 18^\circ C$ for a time $t_e$. |
| **DHCA**          | Circulation is stopped at a time $t_{CA} = t_{cool} + t_e$ and the temperature distribution is calculated for times exceeding the HMI of Eq. 5.5. |
| **Rewarming**     | Circulation is restarted at time $t_{CA} + \Delta t_{CA}$ and continued for a time $t_{warm}$. |
Table 5.3: Physical and physiological parameters for the 3-layer head model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brain</th>
<th>Bone</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_i \ (W/m^2C)$ [27]</td>
<td>0.50</td>
<td>0.410</td>
<td>0.215</td>
</tr>
<tr>
<td>$\rho_i \ (kg/m^3)$</td>
<td>1050</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>$c_i \ (J/kg^2C)$ [95]</td>
<td>3700</td>
<td>2300</td>
<td>4000</td>
</tr>
<tr>
<td>$W_o \ (ml/100 \ grs \ of \ tissue/min)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>50.0</td>
<td>0.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Child</td>
<td>25.0</td>
<td>0.1</td>
<td>2.0</td>
</tr>
<tr>
<td>$CMRO_2 \ (ml/100 \ grs \ of \ tissue/min)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Child</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\sigma_m \ (W/m^3)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>10,437.0</td>
<td>368.3</td>
<td>363.4</td>
</tr>
<tr>
<td>Child</td>
<td>5869.3</td>
<td>368.3</td>
<td>363.4</td>
</tr>
<tr>
<td>Layer thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>85.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Child</td>
<td>53.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

For the blood, $c_b = 3800 \ J/Kg^2C$, and $\rho_b = 1050 \ Kg/m^3$. 
time defined before. When the blood flow is discontinued, the metabolic rate decreases exponentially with time \([29]\) following the relation

\[
q_m = q_m^0 Q_{10}^{(T - T_\infty)/10} \exp \left( - (t - t_{CA}) / \tau \right)
\]  
(5.4)

where \(T_o\) represents the normal systemic or arterial temperature, and \(\tau\) is a reference time that corresponds to the safe duration of DHCA at \(37^\circ C\) and is between 3 and 5 minutes.

In the simulations, the circulatory arrest is prolonged outside the safe duration time or hypothermic metabolic index (HMI) \([24]\), which is calculated using the average \(Q_{10}\) and the relation

\[
HMI = \frac{\tau}{Q_{10}^{(T - T_\infty)/10}},
\]  
(5.5)

where \(\tau\) and \(T_o\) have the same meaning as before.

The final stage in the calculations corresponds to reperfusion and rewarming, and two different cases are considered. The first case corresponds to "warm reperfusion", which is characterized by the introduction of the blood perfusate at normal systemic temperature \((T_a = 37^\circ C)\); the other case is similar to the systemic cooling described before, and consists in introducing cool blood \((T_a = 18^\circ C)\) and increase its temperature at different speeds \(m_{\text{warm}}\).

In the calculations, fixed external skin temperature \((h \to \infty)\) and external convection are studied. Different cooling conditions are considered to analyze the effect that external cooling has on the temperature distribution during the arrest period, and to show how the internal temperature gradients can be controlled by using the appropriate external cooling conditions. The case of fixed external skin temperature corresponds to using a cooling helmet on the head, and the external convection cases studied use \(h= 2\) and \(10\ W/m^2{^\circ C}\), and correspond to still air and air moving at a speed of \(10\ m/s\) \([5]\), respectively.
5.2.1 Systemic Hypothermia

For the calculations during systemic cooling or hypothermic cardiopulmonary bypass, three different blood cooling rates \( m \) are considered: \( m = 0.950, 0.633, 0.475 \, ^\circ C/min \), which correspond to an arterial blood temperature change from \( 37^\circ C \) to \( 18^\circ C \) in a time \( t_{cool} \) of 20, 30 and 40 min, respectively, as given by Eq. (5.5). Figs. 5.7 and 5.8 present the temperature history of the deep tissue and the skin surface for adults and children subjected to three different blood cooling rates \( m \); in these figures it is observed that longer cooling periods produce smaller temperature gradients within the tissue layers.

As expected from the differences in blood flow within each tissue layer, Fig. 5.7 shows that the time required to cool the external tissues is larger than the time required to cool the brain tissue. Also, Fig. 5.7 shows that independently of the cooling rate \( m \), the temperature distribution in an adult head reaches the equilibrium configuration after 30 minutes of stabilization (i.e. \( t_e > 30 \text{min} \)); and it is observed that variations of the MAPB from 70 to 35 mmHg do not increase the cooling time considerably.

Fig. 5.8 shows the calculations using the geometric and physiologic parameters for children and the same blood cooling rates (\( m \)) used in the calculations for adults. In this figure one observes that the internal and the external tissue layers cool at the same rate. Comparing Figs. 5.7 and 5.8, one observes that, as a result of the reduced CBF of children, the temperature drop at the various tissue layers is smaller in children than it is in adults. Also as a result of the lower cerebral blood flow in children, the equilibration time required by children is longer than the time required by adults.

From previous studies [40, 41], we concluded that external or superficial cooling of the head was insufficient to reduce brain temperature due to the high cerebral blood flow. Consequently, the best way to achieve brain cooling is by lowering the arterial blood temperature. Figs. 5.7 and 5.8, present the temperature variations during the
Figure 5.7: Temperature history for the deep brain tissue and the skin surface in adults at three different cooling rates $m = 0.950^\circ C/min$ (solid), $0.633^\circ C/min$ (−), $0.475^\circ C/min$ (−−). For the case of external convection ($h = 2\ W/m^2^\circ C$ and $T_\infty = 20^\circ C$).

Figure 5.8: Temperature history for the deep brain tissue and the skin surface in children at three different cooling rates $m = 0.950^\circ C/min$ (solid), $0.633^\circ C/min$ (−), $0.475^\circ C/min$ (−−). For the case of external convection ($h = 2\ W/m^2^\circ C$ and $T_\infty = 20^\circ C$).
Figure 5.9: Temperature history for the deep brain tissue and the Bone/Brain interface in adults at three different cooling rates $m = 0.950^\circ C/\text{min}$ (solid), $0.633^\circ C/\text{min}$ (–), $0.475^\circ C/\text{min}$ (––). For the case of fixed external skin temperature ($h \to \infty$, $T_{\text{skin}} = 18^\circ C$)

hypothermic CPB, and show how external structures are cooled at a slower rate than the deep tissue. To cool at the same rate all the tissue layers during cardiopulmonary bypass, the skin surface is kept constant ($h \to \infty$) and set to $18^\circ C$. Fig. 5.9 shows the temperature variations when the external skin is cooled and maintained at a temperature close to that of the perfusate; in this figure it is observed that all tissue layers cool approximately at the same rate despite the differences in the characteristic blood flow of each layer.

### 5.2.2 Circulatory Arrest

Depending on the cooling rate $m$ employed during the first stage, adults and children require different amounts of time to reach the equilibrium configuration. In this study, circulatory arrest (CA) is started at different times ($t_{\text{CA}} = t_{\text{cool}} - t_e$) during the equilibration period following blood cooling. In the cases studied, the cooling rate employed in the systemic cooling stage is $m = 0.633^\circ C/\text{min}$, and the blood
flow is discontinued after 10 and 30 minutes of stabilization in adults and after 10 and 40 minutes of stabilization in children. In these calculations, external convection ($h = 2W/m^2 \, ^\circ C$) and fixed skin temperature ($h \to \infty$) are considered. In order to see the temperature variation in the deep brain tissue during prolonged circulatory arrest, the duration of the circulatory arrest in the calculations presented here exceeds the safe limit calculated with Eqn. (5.5). Circulation is stopped at different equilibration times to observe the effect that departing from a temperature distribution far from equilibrium has on the deep brain temperature during extended periods of lack of blood flow, and the objective is to determine whether the cooling time and rate of cooling are determinant factors to the success of hypothermia.

Since small temperature gradients are necessary to reduce the possibility of tissue necrosis [1]; in the calculations, the circulatory arrest is started from two different temperature distributions, one close to the steady state configuration (after 30 minutes of stabilization or more, i.e. $t_e \geq 30 \text{ min}$) and the other after a short equilibration time of $t_e = 10 \text{ minutes}$. These calculations present the importance of departing from a near steady state temperature distribution when DHCA is started, and the effect of external cooling during hypothermic circulatory arrest. In the calculations, the circulation is stopped for up to 45 minutes in adults and up to 80 minutes in children and the temperature evolution of different points in the head is observed.

The temperature variations during CA in adults for the case of $h = 2 \, W/m^2 \, ^\circ C$ are presented in Figs. 5.10-5.11. These figures show the time variations the temperature at points located at the skin/bone interface, the Bone/Brain interface, and two points in the brain tissue located 1cm and 2cm below the Bone/Brain interface. Figs. 5.10-5.11 show that the tissue temperature decreases with the tissue depth, and that as time progresses the deep brain tissue increases its temperature because there is no blood flow to cancel out the small amount of metabolic heat produced by the tissue. On the other hand, in the skin and bone layers the temperature decreases with time because of the low tissue metabolic activity, and the effect of the external cooling
Figure 5.10: Temperature history during circulatory arrest in adults for the case of external convection \((h = 2 \text{ W/m}^2 \cdot \text{°C})\) and \(T_\infty = 20\text{°C}\). Blood flow was stopped after 10 minutes of equilibration.

Figure 5.11: Temperature history during circulatory arrest in adults for the case of external convection \((h = 2 \text{ W/m}^2 \cdot \text{°C})\) and \(T_\infty = 20\text{°C}\). Blood flow was stopped after 30 minutes of equilibration.
Figure 5.12: Temperature history during circulatory arrest in adults for the case of fixed external skin temperature ($h \to \infty$ and $T_{\text{skin}} = 18^\circ C$). Blood flow was stopped after 30 minutes of equilibration.

condition.

Comparing Figs 5.10 and 5.11, one notes that the increment in the deep tissue temperature during the circulatory arrest is larger when the blood circulation is stopped far from the equilibrium configuration ($t_e < 30$ min). The effect that the initial temperature distribution has over the temperature evolution during DHCA explains why some times hypothermia has deleterious effects.

Once the importance of departing from a steady state temperature distribution during DHCA has been established, the effect of the external boundary condition is analyzed by considering the case of convection to still air ($h = 2{\text{ W/m}}^2{\text{ }^\circ C}$) and fixed skin temperature ($h \to \infty$, $T_{\text{skin}} = 18^\circ C$). Fig. 5.12 shows the temperature history during CA for adults after 30 minutes of equilibration when the skin surface is kept constant at $T_{\text{skin}} = 18^\circ C$. In this figure, one notes that the temperature gradients within each tissue layer are small; the temperature at every tissue layer increases in the first 5 minutes, due to the time dependence of Eqn. 5.4; and for longer times the temperature decreases, due to the cooling effect of the external boundary condition.
Figure 5.13: Temperature history during circulatory arrest in children for the case of external convection \((h = 2 W/m^2 °C\) and \(T_\infty = 20°C\)). Blood flow was stopped after 40 minutes of equilibration.

Figure 5.14: Temperature history during circulatory arrest in children for the case of fixed external skin temperature \((h \to \infty \text{ and } T_{\text{skin}} = 18°C)\). Blood flow was stopped after 40 minutes of equilibration.
Comparing Figs. 5.11 and 5.12, the effect of the boundary condition is observed, and it is seen that the external cooling during DHCA helps reduce the temperature gradients within the head. Also it is observed that in the absence of normal blood flow and under hypothermic condition, the external boundary condition affects the temperature distribution contrary to previous observations [40, 41] made in normothermia and under normal blood flow.

Similar calculations during CA were performed for children, using the parameters of Table 5.1. The temperature variation during circulatory arrest obtained for the convection to still air, and the fixed skin temperature cases are presented in Figs. 5.13 and 5.14, respectively. In these figures, the temperature variation at the skin/bone interface, the Bone/Brain interface, and two points at the brain tissue is presented. For children, the safe duration time of circulatory arrest at 18°C is about 60 minutes, and the calculations during DHCA are extended to 80 minutes. The initial temperature distribution used in these figures corresponds to the head temperature calculated after 20 minutes of systemic cooling ($t_{cool} = 20$ min) and 40 minutes of stabilization ($t_e = 40$ min) for each one of the external boundary conditions considered for adults.

In Fig. 5.13 it is observed that, the deep tissue temperature increases as the DHCA progresses, and that the bone and skin layers cool down in the process. Fig. 5.14 shows the temperature variations when the skin temperature is kept constant at 18°C, in this case the deep tissue temperature decreases with time. Figs. 5.13 and 5.14 show the same behavior discussed previously for adults; but in this case, the time required to reach equilibrium configuration and the safe duration of the CA are longer than in adults due to the differences in blood flow and metabolic rate.

### 5.2.3 Rewarming

In this stage, blood flow is reinitiated after a time $\Delta t_{CA}$ that corresponds to the "safe" duration time calculated with Eqn. 5.5. During warm reperfusion, the blood entering the body is at the normal arterial temperature, and cold reperfusion is characterized
Figure 5.15: Temperature history during rewarming in adults for external convection \( h = \frac{W}{m^2 \circ C} \) and \( T_{\infty} = 20^\circ C \) and different rewarming strategies: 1) Cold reperfusion (solid) and 2) various rewarming rates \( m = 0.950, 0.633, \) and \( 0.475 \)

by introducing blood which temperature increases from \( 18^\circ C \) to \( 37^\circ C \) in a time \( t_{\text{warm}} \), as in the systemic cooling case.

During rewarming it is observed that warm reperfusion allows to reach the steady state configuration faster, but the temperature gradients are larger. On the other hand, cold reperfusion gives smaller temperature gradients during the rewarming period \( \left(t_{\text{warm}}\right) \), but an equilibration time of up to 30 minutes in adults and 60 minutes in children is necessary to achieve thermal equilibration after blood is reintroduced to the head. The temperature variations in an adult subjected to different rewarming strategies is presented in Fig. 5.15. In children, the equilibration time required after the different rewarming rates almost doubles due to the characteristic blood flow of children.

5.2.4 Summary of Results

Longer cooling times \( t_{\text{cool}} \) during systemic cooling produce smaller temperature gradients within tissue layers during systemic cooling. It is observed that the time required
to reach an equilibrium temperature distribution after hypothermic CPB is longer in children and in the external tissue layers due to the small blood volume characteristic of these tissues. For a cooling rate of $m = 0.950 \degree C/min$, the equilibrium temperature distribution is achieved after 30 min of stabilization in adults and, about 60 minutes in children.

In adults and children, it is observed that the temperature variation within each tissue layer during circulatory arrest is small if the blood flow is stopped when the temperature distribution is close to thermal equilibrium. Our calculations show that if the blood flow during DHCA is stopped far from an equilibrium temperature distribution, the tissues have not been properly cooled down and the temperature in the deep brain tissue raises due to the residual metabolic activity, canceling the beneficial effect of hypothermia.

Contrary to previous observations during normothermia, the simulations presented here also show that external cooling has a considerable effect during hypothermia and lack of blood flow, and can be used to better control the brain temperature during CA. The calculations presented shown that when the external skin temperature is set at a temperature close to the target cooling temperature (18$\degree C$), the temperature gradients during the circulatory arrest are reduced, and the deep brain temperature decreases with time. The calculations show that external cooling during DHCA can help to reduce the residual cerebral metabolism ensuring the protective effect of hypothermia.

Finally, using warm reperfusion the normal head temperature distribution is restored rapidly, but large temperature gradients are observed within the head. Cold reperfusion, instead produces small temperature gradients and to make sure that all tissue layers in the head reach a stable temperature it is necessary to maintain CPB at the normal arterial temperature for up to 30 min in adults and considerable more time in children.
Chapter 6

Model Validation using Data for Swine

Brain temperature is an important variable to understand the response of the brain to injury [35, 37], and reductions in brain temperature of 2-4°C are known to provide neuroprotection after hypoxia-ischemia [9, 16]. However, the measurement of brain temperature is an invasive procedure. As a result, the development of thermal models that accurately predict deep brain temperature is extremely useful and important due to the therapeutic implications of hypothermia.

This chapter details the use of a thermal model that incorporates measurements of the cerebral blood flow (CBF), the cerebral metabolic rate of oxygen consumption $CMRO_2$ and the arterial temperature ($T_a$) recorded during experiments that analyze the brain temperature variation in swine during conditions such as cerebral ischemia or hypothermia. The calculations presented in this chapter are performed to validate the thermal model described in Chapter 4. All the measurements presented within this chapter were obtained by Dr. Laptook and collaborators, and correspond to published experimental results which analyze the effect of whole body cooling versus selective head cooling strategies on the deep brain temperature [38]; and to unpublished results of experiments dealing with the temperature changes produced by cerebral ischemia [36]. The temperature, CBF and $CMRO_2$ measurements of this last experiment are included in the Appendix B.

In this section, the time dependent temperature distribution during selective and whole body cooling are calculated using the layered head model described in Chapter 4 and refs. [40, 41] and the geometric data of a swine shown in Table 6.1. The calculations incorporate measurements of the arterial temperature, the cerebral blood
Table 6.1: Physical and physiological parameters for the 3-layer head model

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Bone</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_i$ ($W/m^oC$)</td>
<td>0.50</td>
<td>0.410</td>
<td>0.215</td>
</tr>
<tr>
<td>$\rho_i$ ($kg/m^3$)</td>
<td>1410</td>
<td>1150</td>
<td>1060</td>
</tr>
<tr>
<td>$c_i$ ($J/kg^oC$)</td>
<td>3700</td>
<td>2300</td>
<td>4000</td>
</tr>
<tr>
<td>Layer thickness (mm)</td>
<td>33.0</td>
<td>1.1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

For the blood, $c_b = 3800$ $J/Kg^oC$, and $\rho_b = 1050$ $Kg/m^3$.

Flow and the cerebral metabolic rate of oxygen consumption $CMRO_2$, which vary with time ([38], Appendix B).

The numerical values for the specific heat of blood and the other tissue layers were assumed equal in magnitude to those reported for humans [95], and are presented in Table 6.1. Variations in the magnitude of the tissue heat capacities were observed in the literature, but these variations had little effect on the calculations. The thermal conductivity values $k_i$ given in Table 6.1 were found in a compilation of tissue thermal conductivity values of different species and tissues [27]. The density of the different tissue layers ($\rho_i$) and the tissue thicknesses ($r_i$) were measured by Dr. Laptook and collaborators at the UT Southwestern Medical Center.

6.1 Physiological Considerations

The thermal model implemented here uses the linear relation observed between blood flow and cerebral metabolic rate of oxygen consumption [73]; It also assumes that the tissue metabolic heat generation $q_m$ and blood flow $W_b$ depend exponentially on the tissue temperature following the $Q_{10}$ law, and that the tissue metabolic heat is proportional to the tissue metabolic rate $MRO_2$ as given by equations (4.4)-(4.5) and 4.2, respectively. For adult swine, it has been reported that the $Q_{10}$ or van’t
Hoff temperature coefficient has a value of $Q_{10} = 2.8$ [85], and this value varies with the thermal conditions affecting the animal, such as hypothermic cardiopulmonary bypass [52, 24].

The average blood perfusion $W_o$ for each tissue layer (brain, bone and skin) during the control period is shown in Table 6.3. The blood flow of the brain tissue was taken from the experiments dealing with ischemia (Appendix B Table B.1), or from the cooling experiments discussed in [36]. The blood flow associated to the bone and skin layers is unknown, but is assumed to be smaller than the average cerebral blood flow, and its value is adjusted to reproduce the control or initial temperature distribution in each one of the experiments considered here. For the brain tissue, the experimental measurements of the cerebral blood flow CBF and the rate of oxygen consumption $CMRO_2$ are used to determine a linear relation of the form

$$CBF = a \cdot CMRO_2 + b.$$  

(6.1)

Which agrees with experimental observations [73]. In Eqn. 6.1, the parameters $a$ and $b$ vary in each experiment as seen in Table 6.2. In this study, it is assumed that the arterial temperature $T_a$ is equivalent to the rectal temperature, which variation in time is known form direct measurement.

It was observed that cerebral blood flow varies in magnitude with the tissue depth [38]. The observed trend indicates that the CBF in the first centimeter is higher than the average CBF of Table 6.3 and then decreases in deeper regions. However, depending on the cooling strategy the blood flow distribution changes [38]. In the experiments employed here, only the time variation of the cerebral blood flow and the $CMRO_2$ are measured (see Tables 6.3, 6.4 and Table B.1). As a result, the blood perfusion $W_b$ and metabolic activity $q_m$ associated to the skin and bone tissue layers are unknown, but they are assumed to vary proportionally to the average CBF and the $CMRO_2$, and their initial magnitude is set to reproduce the control temperature measurements of each experiment.

Given the linear relationship between blood flow and metabolic activity of Eqs.
Table 6.2: Relationship between CBF and CMRO₂ for the different experiments performed on swine

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia (Appendix A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>20.25</td>
<td>-10.90</td>
<td>0.93</td>
</tr>
<tr>
<td>One month</td>
<td>26.03</td>
<td>-25.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Head cooling [38]</td>
<td>16.7</td>
<td>3.4</td>
<td>0.92</td>
</tr>
<tr>
<td>Body cooling [38]</td>
<td>13.0</td>
<td>10.0</td>
<td>0.89</td>
</tr>
</tbody>
</table>

* b is measured in mL/min/100g

Table 6.3: Control average blood flow in each tissue layer for the different experiments performed in swine.

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Bone</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia (Appendix A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>50 ± 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One month</td>
<td>66 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooling Experiments[38]</td>
<td>75 ± 29</td>
<td>15 ± 5</td>
<td>50 ± 15</td>
</tr>
</tbody>
</table>

The units of the blood flow are (mL/min/100g)

Table 6.4: Variations in the regional CBF during different cooling strategies

<table>
<thead>
<tr>
<th></th>
<th>1st cm</th>
<th>2nd cm</th>
<th>3rd cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>85 ± 35</td>
<td>60 ± 29</td>
<td>67 ± 20</td>
</tr>
<tr>
<td>Whole Body Cooling</td>
<td>30 ± 15</td>
<td>33 ± 15</td>
<td>38 ± 17</td>
</tr>
<tr>
<td>Selective Head Cooling</td>
<td>51 ± 25</td>
<td>41 ± 20</td>
<td>40 ± 20</td>
</tr>
</tbody>
</table>

The regional cerebral blood flow is measured in mL/min/100g
(6.1), and (4.2), \( q_m^a(r,t) \) for the brain tissue, has the form

\[
q_m^a(r,t) = \epsilon \rho(r) \frac{CBF(r,t) - b}{a},
\]

(6.2)

where \( a \) and \( b \) are given in Table 6.2, and \( CBF(r,t) \) corresponds to the regional cerebral blood flow measured at different times during the experiments.

On the other hand, for the bone and skin layers, \( q_m^a(r,t) \) is assumed to vary proportionally to the \( CMRO_2 \)

\[
q_m^a(r,t) = q_o(r) \frac{CMRO_2(t)}{CMRO_2^2},
\]

(6.3)

where \( q_o(r) \) corresponds to the average metabolic heat released by the tissue (bone or skin) at the normal or control temperature and it is assumed constant within each tissue layer; \( CMRO_2 \) represents the cerebral metabolic rate of oxygen consumption measured at time \( t \) during the experiment, and \( CMRO_2^2 \) represents the measurement of the oxygen consumption at the beginning of the experiment or also referred as "control".

Equations (6.1), (6.2), and (6.3), introduce the temporal changes observed in the cerebral blood flow and the metabolic activity of swine subjected to either ischemia or to different cooling strategies. These equations are incorporated in the system of equations (4.10) to analyze the effect of blood flow variations in the brain temperature distribution.

### 6.2 Mathematical Model Results

The numerical calculations presented in this section were performed to reproduce the temperature variation observed experimentally in swine experiencing ischemia, selective head cooling, and whole body cooling. In the calculations, the skin temperature varies following the experimental measurements. The initial condition in the calculations corresponds to the steady state temperature distribution [40, 41] obtained using the control values of blood flow and arterial temperature, as well as the constant
parameters of Table 6.1. The metabolic activity and blood perfusion in the bone and skin layers are set to match the initial or control temperature distribution in each experiment.

From previous studies [40, 41], it is known that the temperature in the deep brain is affected largely by the mean arterial temperature \( T_a \), the magnitude of the cerebral blood flow, and the metabolic heat generation of the brain tissue. The deep tissue temperature depends directly on the arterial temperature \( T_a \). In the calculations presented here, the arterial and rectal temperature are considered equal. This assumption neglects the possibility of countercurrent cooling of arterial blood, which is known to occur in the swine.

The following results correspond to the analysis of the brain temperature during selective head cooling, whole body cooling, and when swine of different ages experience ischemia. To provide estimates of the brain temperature for the different situations considered experimentally, the calculations were performed using the central value and the upper and lower limits of the experimental measurements of blood flow, skin temperature and arterial temperature given in the Appendix B and Ref. [36].

6.2.1 Temperature Calculations during Different Cooling Strategies

In this section, the temperature distribution and its time variation are calculated for two different cooling cases: whole-body cooling, and selective head cooling. For the calculations, the core body temperature, the skin temperature, the regional cerebral blood flow variations, and the relation between cerebral blood flow and metabolic rate of oxygen consumption are taken from Ref. [36]. It is assumed that the blood flow reaches its steady state value (Table 6.4) after 30 minutes of cooling, and it remains constant for the rest of the experiment; it is also considered that the regional blood perfusion decreases linearly with time during the 30 minute cooling phase.

With whole body cooling, the arterial temperature is varied from the control value of 38.5°C to 34.5°C in a time interval of 30 minutes. The calculated temperature is
Figure 6.1: Temperature history, for various depths $d$ during whole-body or systemic cooling

presented in Fig. 6.1, and it is obtained using the direct skin temperature measurement reported in [36], and the layer blood perfusion given in Tables 6.3 and 6.4. Fig. 6.1 shows the temperature variation of several observation points $d$ located at the skin, at the Bone/Brain interface and at a depth of one centimeter (Brain 1cm) and two centimeters (Brain 2cm) within the brain tissue.

From Fig. 6.1, it is observed that the temperature at the different points $d$ reaches a constant value after the 30 minutes of cooling, and that the temperature difference between adjacent observation points remains constant during the cooling period. This behavior agrees with the experimental observations. The average temperature difference between the Bone/Brain interface (dura) and a point 2 cm below it (Brain 2cm) is $1.05 \pm 0.30 \degree C$.

Comparing the calculations with the direct measurements, it is observed that the calculated temperatures drop as a result of the cooling for the deep brain tissue (Brain 2cm and Brain 1cm) is smaller than the reported experimental values. However, the measurement falls within the temperature calculated using the upper and lower values
Figure 6.2: Temperature history during whole-body or systemic cooling, for a) A point located 1 cm below the Bone/Brain interface, b) The Bone/Brain interface. The solid line indicates the calculation using the central values, ( - - ) indicates the calculation using the upper limit values, and ( - . ) indicates the lower limit values.

of \( T_a \), \( CBF \) and \( T_{skin} \), as shown in Fig. 6.2.

The calculated temperature for the head cooling case is shown in Fig. 6.3. During head cooling, the arterial or core body temperature is kept constant through all the experiment, and the skin temperature varies dramatically due to the surface cooling of the head. For head cooling case, the temperature gradients are larger than those observed during whole body cooling. The temperature difference between the Bone/Brain interface and the observation point \( Brain \ 2cm \) is 6.76 ± 3.50 °C.

The thermal model is able to reproduce the over all behavior and temperature changes observed experimentally during systemic and selective head cooling. But, the calculated temperature at the deep tissue \( (i.e. \ at \ the \ observation \ points \ Brain \ 2cm \ and \ Brain \ 1cm) \) is greater than the measurement, and the temperature at the Bone/Brain interface is lower than the reported. On the other hand, the temperature gradients between the Bone/Brain interface and the observation point \( Brain \ 2cm \) agree well with the values reported in [38].
Figure 6.3: Temperature history during selective head cooling for various depths $d$.

Figure 6.4: Temperature history during selective head cooling, for a) A point located 1 cm below the Bone/Brain interface, b) The Bone/Brain interface. The solid line indicates the calculation using the central values, (−−) indicates the calculation using the upper limit values, and (−−−) indicates the lower limit values.
6.2.2 Temperature Calculations during and after Ischemia

In this section, the temperature history for swine experiencing ischemia is calculated using the mathematical model described before, and the experimental measurements of cerebral blood flow, metabolic activity and arterial temperature given in Appendix B. In these calculations, the arterial and skin temperature variations are taken from Figs. B.1 and B.2 for newborns and one month old animals, respectively.

Figs. 6.5 and 6.6 represent the calculations using the central values of the experimental measurements of \( CBF \), \( CMRO_2 \) and \( T_a \). In these simulations, as the blood flow decreases the tissue cools down, and vice versa, which corresponds to the tendency observed in the experiment. In the experiments dealing with ischemia it is observed that the regional cerebral blood flow varies uniformly across the brain tissue, similar to the case of selective head cooling, where the regional cerebral blood flow is reduced 60\% with respect to the control value, as seen in Table 6.4.

For the one month old swine, the calculated temperature history is given in Fig. 6.6. In this case, the layer thicknesses associated to older swine are 49.5 mm, 2.2 mm, and 3.2 mm for the brain, bone and skin layer, respectively. For every point \( d \), the temperature in the older animals is larger than the temperature of newborns as expected from the larger values of arterial temperature and metabolic rate.

Comparing the numerical results given in Figs. 6.5 and 6.6 with the experimental measurements of Figs. B.1 and B.2, we observe that the calculations give temperatures at the Bone/Brain interface below the measured values, but these values lay inside the uncertainty region delimited by the experimental error.

Figs. 6.7 and 6.8 show the calculated temperature history for the points Bone/Brain and Brain 1cm in the newborn and one month old swine, respectively. In these figures, the upper dashed line (- -) is obtained using the upper limit values \( (X + \delta X) \) of \( CBF \), \( CMRO_2 \), and \( T_a \); the solid line corresponds to the calculations using the central values (Figs. 6.5 and 6.6 ), and the lower curve ( - ) is generated using the lower limit values \( (X - \delta X) \). Comparing these figures, with Fig. B.1 and B.2, we
Figure 6.5: Temperature history, for the newborn swine at various depths \( d \). The vertical broken lines indicate the interval of brain ischemia.

Figure 6.6: Temperature history, for the one month old swine at various depths \( d \). The vertical broken lines indicate the interval of brain ischemia.
Figure 6.7: Temperature history for the newborn swine at a) the Bone/Brain interface and b) a point 1cm below the brain cortex (Brain 1cm). The solid line indicates the calculation using the central values, (---) represents the calculation using the upper limit values, and (--) corresponds to the lower limit values.

observe that the calculated interval falls within the uncertainty region observed in the experiments, and that the magnitude of the temperature drop after ischemia is not affected considerably when the CBF, CMRO₂ or Tₐ vary in the range given in Table B.1.

It is observed that variations in the arterial temperature affect more drastically the deep brain tissue temperature than the temperature of the bone and the skin. The temperature in the external tissue layers is highly affected, on the other hand, by variations in the blood flow volume and the external skin temperature as can be seen in Table B.1.

In Figs. 6.5 and 6.6, the maximum temperature drop occurs at the end of the ischemic period indicated by the broken lines. Table 6.5 shows the maximum temperature drop calculated for the newborn and one month old swine. In this table, one observes that the maximum temperature drop (max ΔT) occurs at the bone brain interface independently of the animal age, and that the temperature drop is larger in
Figure 6.8: Temperature history for the one month old swine at a) the Bone/Brain interface and b) a point 1cm below the brain cortex (Brain 1cm). The solid line indicates the calculation using the central values, (-) represents the calculation using the upper limit values, and (--) corresponds to the lower limit values.

The newborn swine than in the older animals as observed experimentally. Comparing with the direct measurements of Appendix B, it is observed that the temperature drop calculated is smaller than the measured value in both animals.

The fact that the calculated temperature drop for newborns is larger than the max $\Delta T$ calculated for the one month old swine depends mostly on the larger arterial temperature variation recorded in newborns, because as seen in Table B.1, the cerebral blood flow and the metabolic rate vary approximately the same percentage in both animals and the variation of the skull and the scalp thicknesses with age is considered.

6.2.3 Discussion of this Section Results

In the calculations, the metabolic heat and blood flow in the bone and skin tissues were approximated to fit the temperature distribution at the beginning of each one of the experiments considered in this work. It was also observed that variations in the tissue heat capacity $c_p$ did not affect the temperature distribution considerably, but
Table 6.5: Maximum temperature drop (max $\Delta T$) for different observation points $d$ in the newborn and the one month old swine

<table>
<thead>
<tr>
<th></th>
<th>max $\Delta T$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Newborn</td>
</tr>
<tr>
<td>Brain 1cm</td>
<td>0.40</td>
</tr>
<tr>
<td>Brain 2cm</td>
<td>0.68</td>
</tr>
<tr>
<td>Bone/Brain</td>
<td>1.37</td>
</tr>
</tbody>
</table>

Variations in the thermal conductivity $k$ of the bone and skin could affect considerably the temperature at the Bone/Brain interface (dura); for instance, an increase of 50% on the thermal conductivity of the skin augmented the temperature in the Bone/Brain interface about 0.4 °C.

From the calculations it is noted that the temperature in the deep tissue depends mostly on the arterial temperature and the cerebral metabolic heat $q_m$ and less on the blood flow. In the calculations, the maximum temperature drop in all the the different experiments considered occurs at the Bone/Brain interface, and agrees with the direct temperature measurements of Appendix B and Ref. [36].

The thermal model reproduced the general trend in the temperature changes observed experimentally during whole and selective head cooling. The temperature gradients between the Bone/Brain interface and the observation point Brain 2cm agree with the values reported in [38]. However, the calculated temperature drop as a result of cooling at the deep brain tissue is lower than the measurements.

The calculations corresponding to the experiments involving ischemia show that the tissue temperature drops as a result of the blood flow reduction, but the temperature change calculated is below the reported in Appendix B. The calculations show that the temperature gradient is larger in newborn animals than in the older swine,
which agrees with the experimental observations. The larger temperature change registered in the newborn swine is due to the reduction in the arterial temperature that these animals experience. The low temperature drop calculated during ischemia, for both newborn and one month old swine, could indicate the existence of a regulatory mechanism that couples $q_m$ not only to the metabolic rate of oxygen consumption as noted in (4.2), but to other physiological parameters, such as variations in the cerebral blood flow, ion concentrations [25], or ATP depletion [84, 93].

6.3 Chapter Summary

A layered head model, that incorporates experimental measurements of arterial temperature, blood flow and metabolic rate of oxygen consumption, was used to reproduce and analyze the temperature drop observed in swine during and after ischemia, and during different cooling strategies. The model is able to reproduce the trends observed in all the experiments considered herein. This study shows the importance of incorporating direct measurements of variables that heavily influence the brain temperature, such as the blood flow, the tissue oxygen consumption, and the arterial temperature.

Slight differences between the calculated temperature values and the direct measurements are observed. These variations are associated to the uncertainty of different parameters such as the thermal conductivity, the tissue metabolism and the bone and skin blood flow.

Further experimentation is necessary to fully understand brain energy metabolism, its relation to age, and the factors affecting the tissue metabolic heat during ischemia. These studies will help to reveal relations between blood flow and metabolic activity and the temperature changes occurring in the tissue. It is also necessary to mathematically model and solve inverse problems using experimental data to estimate parameters like tissue metabolic heat and blood flow in external layers. Finally, measurement of the thermal conductivity of the different tissue layers is necessary to
successfully reproduce the direct temperature measurements.
Chapter 7

Calculations using the Realistic 3D Model

In this chapter, the realistic 3D-model described in Section 4.3 is used to determine the brain temperature for the case of global and local ischemia. Global ischemia is modeled during circulatory arrest and asphyxia, and focal ischemia is produced by reducing blood flow and metabolic activity in a selected region of the brain tissue. In both cases, selective head cooling and whole body cooling are analyzed. The results presented in this chapter are published in [42] and [44].

7.1 Temperature Calculations during Global Ischemia

In this chapter the temperature distribution in the head and neck of an adult male is calculated during selective head cooling, whole body cooling, and circulatory arrest. The tissue temperature is obtained using the thermal model that incorporates temperature dependent blood flow and metabolic activity described in Chapter 4. Selective head cooling is achieved by either forced convection or contact cooling at the skin surface. Whole body cooling is produced by varying the arterial blood temperature using extracorporeal perfusion or cardiopulmonary bypass (CPB), where the heart is stopped and perfusion is assisted by a heart-lung machine that oxygenates, and reinfuses the blood into the body at a temperature $T_a$. Finally, the blood circulation is stopped and the effect of different boundary conditions at the skin surface is observed in the temperature distribution at the brain tissue.

The initial temperature distribution used in the calculations presented here corresponds to the steady state temperature distribution calculated for the natural convection case ($h = 5 W/m^2 \circ C$) when temperature of the surrounding air is $T_\infty = 20 \circ C$;
Figure 7.1: Temperature contours at a sagittal plane at the midsection of the head. The contours shown correspond to the steady state distribution calculated for the case of natural convection \((h = 5W/m^2 \cdot ^oC\) and \(T_\infty = 20^oC\)). The temperature value associated to each contour are presented at the right hand side of the figure.

Fig. 7.1 shows the temperature contours at a sagittal plane through the middle of the head for this case. The temperature associated to each one of the contours drawn in Fig. 7.1 is listed for each one of the contours starting at the the center. In this figure, a variation in the spatial temperature gradient between the skin and the deep brain tissue is observed along different directions, such differences are the result of geometry and variations in layer thicknesses.

A summary of the calculations presented herein and the corresponding boundary conditions used in the calculations are shown in Table 7.1. The values used for the convective coefficient \(h\) in the case of natural convection (still air) and cooling by forced convection were taken from [28]. The results presented next correspond to the temperature history of points at various depths within the brain tissue, as shown in Fig. 7.2. These points are located on the midline sagittal plane, at a distance of 1.5, 2.6, 4.5, and 9.5 cm below the skin surface, respectively.

Figures 7.3 and 7.4, show the temperature variation over time for selected points during selective head cooling by forced air convection at the skin surface and contact
Table 7.1: Calculations Performed

<table>
<thead>
<tr>
<th>Case</th>
<th>Boundary Conditions</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state</td>
<td>$h = 5W/m^{2\circ}C$</td>
<td>Not shown</td>
</tr>
<tr>
<td>$T_{\infty} = 20^\circ C$</td>
<td>Forced convection</td>
<td></td>
</tr>
<tr>
<td>Selective head cooling</td>
<td>$h = 30W/m^{2\circ}C$</td>
<td>Fig. 7.3</td>
</tr>
<tr>
<td>$T_{\infty} = 20^\circ C$</td>
<td>Fixed temperature at the skin</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{skin}} = 0, 10, 18^\circ C$</td>
<td></td>
<td>Fig. 7.4</td>
</tr>
<tr>
<td>Whole body cooling</td>
<td>Natural convection</td>
<td></td>
</tr>
<tr>
<td>CPB, $t_{\text{cool}} = 30\text{min}$</td>
<td>$h = 5W/m^{2\circ}C$</td>
<td>Fig. 7.5</td>
</tr>
<tr>
<td>$T_a: 37^\circ C \rightarrow 18^\circ C$</td>
<td>$T_{\infty} = 20^\circ C$</td>
<td>Fixed temperature at the skin</td>
</tr>
<tr>
<td>$T_{\text{skin}} = 18^\circ C$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory arrest after HCPB</td>
<td>Natural convection</td>
<td></td>
</tr>
<tr>
<td>$t_c = 40 \text{ min}$</td>
<td>$h = 5W/m^{2\circ}C$</td>
<td>Fig. 7.7</td>
</tr>
<tr>
<td>$T_{\infty} = 20^\circ C$</td>
<td>Fixed temperature at the skin</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{skin}} = 18^\circ C$</td>
<td></td>
<td>Fig. 7.7</td>
</tr>
</tbody>
</table>
Figure 7.2: Observation points located in a sagittal plane at the midsection of the head. The points are located at 1.5, 2.6, 4.5, and 9.5 cm below the skin surface.

cooling, respectively. Fig. 7.4, shows the temperature variations for three different skin temperatures that correspond to 0, 10 and 18 °C. It is observed that independently of the external boundary condition, only the external points in the brain experience a small temperature reduction due to external cooling. The calculations show the time required by the system to reach a stationary temperature distribution after cooling was performed by either forced convection or contact was started. From Fig. 7.4 it is seen that when cooling the skin surface to 18 °C the time required to achieve temperature equilibration is 20 minutes, whereas when $T_{skin} = 0^\circ C$ the required time is about 40 minutes.

Under normal blood flow to the brain, it has been observed that deep tissue temperature corresponds to the arterial temperature and that selective head cooling only affects the external structures of the brain. Consequently, to decrease the temperature of the deep tissue, the temperature of the arterial blood needs to be reduced by whole body cooling which can be achieved by hypothermic cardiopulmonary bypass or HCPB. Figures 7.5 and 7.6 present the temperature variation of different points in
Figure 7.3: Temperature history during cooling by external convection ($h = 30 \text{ W/m}^2 \text{ °C}$ and $T_\infty = 20\text{°C}$). These lines correspond to the points A to D indicated in Fig. 7.2.

Figure 7.4: Temperature history during surface cooling by contact, for different skin surface temperature: $T_{\text{skin}} = 0, 10, 18\text{°C}$. This figure shows the temperature history of the points A to D indicated in Fig. 7.2.
Figure 7.5: Temperature history during hypothermic cardiopulmonary bypass for \( h = 5 \text{ W/m}^2 \text{ °C}, T_\infty = 20\text{ °C}, \) and arterial blood reduced from 37 to 18 °C in 30 minutes, for the points A to D indicated in Fig. 7.2.

the brain during HCPB for natural convection at the skin surface and skin cooling by contact, respectively. During HCPB, the temperature of the arterial blood is reduced from its normal average value (37°C) to 18°C during 30 minutes (\( t_{\text{cool}} = 30 \text{ min} \)) and then kept constant. Comparing Figs. 7.5 and 7.6, one observes that by varying arterial blood temperature, the temperature of the different points in the brain is reduced uniformly, and that variations in the temperature gradients within the tissue occur as a result of the cooling condition at the skin surface (natural convection or cooling by contact).

Finally, Fig. 7.7 shows the temperature variations during circulatory arrest after HCPB at 18°C for the case of natural convection (solid lines) and fixed skin temperature (dashed lines). The curves of Fig. 7.7 correspond to the time history of points A, C and D, and it is observed that external cooling during hypothermic circulatory arrest can be used to control temperature gradients within the tissue and to reduce
Figure 7.6: Temperature history during hypothermic cardiopulmonary bypass with external skin cooling $T_{\text{skin}} = 18^\circ C$, and arterial blood reduced from 37 to 18 $^\circ C$ in 30 minutes, for the points A to D indicated in Fig. 7.2.

the tissue temperature increment resulting from residual metabolic heat.

7.1.1 Section Summary and Important Remarks

Brain temperature calculations help to understand the factors that affect the outcome of hypothermic therapies. The temperature distribution in the realistic head and neck was calculated for selective head cooling achieved by various the external boundary conditions; whole body cooling through hypothermic cardiopulmonary bypass and for variations in the cerebral blood flow.

The calculations performed for the different cooling strategies show the time required by the system to achieve a stationary temperature distribution for the different cooling strategies considered. It was also observed that deep tissue temperature cannot be reduced effectively during normal blood flow by selective head cooling, and that selective head cooling can be used to affect temperature gradients within tissue
Figure 7.7: Temperature history during deep hypothermic circulatory arrest for natural convection \((h = 5 \text{ W/m}^2 \text{ °C}, T_\infty = 20^\circ \text{C})\) (solid lines) and fixed skin temperature \((T_{\text{skin}} = 18^\circ \text{C})\) (dashed lines), when circulation is stopped after 40 minutes of stabilization. These lines correspond to the points A, C and D indicated in Fig. 7.2.
layers.

The calculations during circulatory arrest shown that when the external skin temperature is set at a temperature close to the target cooling temperature, the tissue temperature gradients during the circulatory arrest are reduced, and the deep brain temperature decreases with time, helping to reduce the residual cerebral metabolism and ensuring the protective effect of hypothermia.

7.2 Temperature Calculations during Focal Ischemia

The objective of this study is to determine the tissue temperature variation resulting from stroke, and to analyze the effect of hypothermia during and after vascular occlusion. For the calculations, the geometrically correct head model described in Section 4.3 is used; blood flow and metabolic activity are selectively reduced in a region of the brain referred as the infarction site; and temporal variations of blood flow and metabolic activity in this region are taken from reported studies of stroke in different animals. Also, mild-to-moderate hypothermia is considered, and the variation in the temperature within the ischemic or infraction site is analyzed when cooling is started during or after the stroke onset.

Several studies have been published in which thermal models have been used to determine the temperature distribution for different cooling strategies and variations in the cerebral blood flow [17, 18, 39, 40, 41, 43, 44]. From these studies only a few incorporate realistic three dimensional geometry of the head and neck [17, 39, 44], and have used a thermal model to study the cerebral temperature variations during circulatory arrest and ischemia and the effect of different cooling strategies in the temperature distribution [18, 43, 44]. In this paper, however, a realistic head model is used for the first time to study the brain temperature variations due to regional ischemia produced by stroke or other type of cerebral vascular occlusion that affects only one section of the brain tissue. The importance of this work lies in the fact that the use of thermal models based in realistic geometry can help to improve the
Table 7.2: Physical and physiological parameters for the head model

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Bone</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_i \ (W/m^\circ C)$</td>
<td>0.50</td>
<td>0.410</td>
<td>0.34</td>
</tr>
<tr>
<td>$\rho_i \ (kg/m^3)$</td>
<td>1050</td>
<td>1500</td>
<td>1000</td>
</tr>
<tr>
<td>$c_i \ (J/kg^\circ C)$</td>
<td>3700</td>
<td>2300</td>
<td>4000</td>
</tr>
</tbody>
</table>

For the blood, $c_b = 3800 \ J/Kg^\circ C$, and $\rho_b = 1050 \ Kg/m^3$

application of hypothermia as well as rewarming techniques used in the treatment of stroke. This is important because cerebral stroke accounts for about 50 percent of neurological problems in general hospitals; it is the third most common cause of death after heart disease and cancer, and controlled hypothermia has been observed to improve the outcome of patients.

7.2.1 Regional Blood Flow and Metabolic Activity Variations

To study the thermal effects of stroke, an ischemic region within the brain tissue is defined, and the thermophysical properties in such region are assumed the same as those of the brain tissue, but blood flow and metabolic activity vary with time during vascular occlusion as will be discussed below. The thermophysical properties for each one of the tissues considered in the calculations are shown in Table 7.2. The mesh used in the calculations is a non structured tetrahedral mesh composed by 6182 nodes and 32352 tetrahedra. The basal metabolic heat and blood perfusion for the brain tissue are $10437 \ W/m^\circ C$ and $50 \ ml/100 \ grs$ of tissue/min, respectively. For the skin/muscle and the bone layers, it is assumed that the metabolic heat and tissue blood perfusion are 15 and 2.5 percent of the cerebral tissue values, respectively and vary proportionally over time.

In the case of stroke or regional ischemia, the infarction site is referred as core,
and the surrounding tissue is called penumbra. In these regions, the blood flow and metabolic activity differ from those of the healthy tissue; in the penumbra, the values of blood flow and metabolic rate are the average those of the core and healthy region. During stroke, the blood flow and metabolic activity in the core and penumbra regions vary with time, and two different stages are identified which correspond to: vascular occlusion and reperfusion as shown in Figs. 7.8 and 7.9. Vascular occlusion generally lasts between one and three hours and blood flow is reduced over 50%. Reperfusion starts with hyperemia or abnormally high regional blood flow, then the blood flow is reduced and returns to the normal value in the following hours or days. In Stage I or vascular occlusion, the blood flow and metabolic activity fall exponentially, following a relationship of the form

\[ W_j(t) = (W_o - W_{sj}) \exp(-t/c\tau_I) + W_{sj}, \quad (7.1a) \]

\[ q_j(t) = (q_o - q_{sj}) \exp(-t/\tau_I) + q_{sj}, \quad (7.1b) \]

where the subindex \( j \) indicates the relation for the core (\( j=1 \)) or penumbra (\( j=2 \)) regions, \( W_o \) and \( q_o \) represent the basal blood flow and metabolic heat and have the same values as the healthy brain tissue, \( W_s \) and \( q_s \) correspond to the value of the blood flow and metabolic heat during the vascular occlusion, and generally have a value of 10 to 50 percent of the basal quantities, \( \tau_I \) is a constant related to the time in which the blood flow and metabolic activity fall during vascular occlusion, and it was assigned a value of 30 minutes; \( c = 0.5 \) and is used to show the delayed reduction in the metabolic rate with respect to the reduction on the blood flow. The values of blood flow and metabolic heat during stroke or vessel occlusion \( W_{sj} \) and \( q_{sj} \) are defined as follows

\[
W_{sj} = \begin{cases} 
  sW_o, & \text{for } j = 1, \\
  \left(\frac{1+s}{2}\right)W_o, & \text{for } j = 2,
\end{cases} \quad (7.2)
\]

\[
q_{sj} = \begin{cases} 
  s\gamma q_o, & \text{for } j = 1, \\
  \left(\frac{1+s\gamma}{2}\right)q_o, & \text{for } j = 2,
\end{cases} \quad (7.3)
\]
Figure 7.8: Cerebral blood flow variations during temporal vascular occlusion (stage I) and reperfusion (stage II). The blood flow in the core was reduced 75% during vessel occlusion.

where \( j = 1 \) denotes the core region and \( j = 2 \) represents the surrounding penumbra. The parameters \( s \) is such that \( 0.1 \leq s \leq 0.25 \) and denotes the reduction on the blood flow during vascular occlusion, \( \gamma \) is a constant parameter used to indicate the reduction on the tissue metabolic rate of the infarct region and takes values of \( \gamma = 1 \) and \( \gamma = 2 \). Different values of \( \gamma \) are considered because during experimental vascular occlusion, rCBF and \( MRO_2 \) might or might not be reduced proportionally. When \( \gamma = 1 \), the blood flow and metabolic activity are said to be coupled, and vice versa.

During reperfusion (Stage II), experiments show that the cerebral blood flow can surpass the basal blood flow value by 180 to 200 percent (hyperemia), and that the tissue metabolic rate can either increase during hyperemia and then return to the ischemic value after several hours or days [19] as seen in Fig. 7.9; or it can maintain its ischemic value for several days [22]. The variations in the blood flow and metabolic
Figure 7.9: Regional cerebral blood flow variations during temporal vascular occlusion (stage I) and reperfusion (stage II). The blood flow and metabolic activity in the core were reduced 75% and 50% ($\gamma = 2$) of the normal value, respectively during vessel occlusion.

The rate in the reperfusion stage are approximated by the following relationships

$$W_j(t) = \begin{cases} 
(W_{max,j} - W_{s,j}) \sin^2(\omega t) + W_{s,j}, & \text{for } t \leq t_{dw} \\
(W_{max,j} - W_{f,j}) \exp\left(-\frac{(t - t_{dw})}{(\kappa_j \tau_2)}\right) + W_{f,j}, & \text{for } t > t_{dw},
\end{cases}$$

(7.4)

$$q_j(t) = \begin{cases} 
(q_{max,j} - q_{s,j}) \sin^2(\phi t) + q_{s,j}, & \text{for } t \leq t_d \\
(q_{max,j} - q_{f,j}) \exp\left(-\frac{(t - t_d)}{2t_d}\right) + q_{f,j}, & \text{for } t > t_d,
\end{cases}$$

(7.5)

were the subindex $j$, and the parameters $W_o$, $q_o$, $W_s$ and $q_s$ represent the same quantities described before; $W_{max}$ represents the hyperemic blood flow, and varies with temperature and occlusion time among other parameters; $t_{dw}$ is the time required to reach the hyperemic blood flow; $t_d$ is the time required to reach the maximum metabolic rate $q_{max}$ observed as a result of the hyperemia. $\omega$ and $\phi$ are defined as $\omega = \pi / 2t_{dw}$ and $\phi = \pi / 2t_d$, respectively. $\kappa_j$ is a constant to adjust the reduction of blood flow after hyperemia in the core and penumbra regions, and $\tau_2$ indicates the
Table 7.3: Values and relationships between the regional blood flow and metabolic rate parameters used in Eqs. 7.1-7.5.

<table>
<thead>
<tr>
<th></th>
<th>Core (j=1)</th>
<th>Penumbra (j=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W_{max}$ (mL/min/100g)</td>
<td>$CBF_M(T)$</td>
<td>$(W_{max1} + W_o)/2$</td>
</tr>
<tr>
<td>$W_f$ (mL/min/100g)</td>
<td>$1.5W_o$</td>
<td>$(W_{f1} + W_o)/2$</td>
</tr>
<tr>
<td>$q_{max}$ (W/m°C)</td>
<td>$0.75q_o$</td>
<td>$1.5q_{o2}$</td>
</tr>
<tr>
<td>$q_f$ (W/m°C)</td>
<td>$1.15q_{s1}$</td>
<td>$1.15q_{s2}$</td>
</tr>
<tr>
<td>$\kappa_j$</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

$W_o = 50$ mL/min/100g, $q_o = 10437$ W/m°C, $CBF_M$ is interpolated from the values in Table 7.4, $\tau_1 = 30$ min, $c = 0.5$, $\tau_2 = 60$ min, $t_d = 60$ min, $t_{dw} = 30$ min, $\omega = \pi/2t_{dw}$ (1/s), $\phi = \pi/2t_d$ (1/s), and $q_{sj}$ is given by Eq. (7.3).

rate at which the blood flow returns to its normal value during reperfusion. $W_f$ and $q_f$ are the final values of blood flow and metabolic activity, respectively after several hours of reperfusion. From experiments it has been observed that $W_o \geq W_f \geq W_s$ and $q_o \geq q_f \geq q_s$. In Table 7.3, the values of the parameters used in equations (7.1)-(7.5) are listed for the core ($j = 1$) and penumbra ($j = 2$) regions. The time changes in the blood flow and metabolic activity and relationship among them considered in the calculations is approximated from reported experiments [70, 19, 22]. The temperature dependence of $W_{max}$ is defined using the percentile changes observed in the metabolic activity and cerebral blood flow that occur in the cat during global ischemia at different temperatures [56]-[57]. For the calculations presented here $W_{max}$ has been approximated using a linear interpolation function and the experimental measurement of blood flow after ischemia [70, 19, 22, 56, 57] noted in Table 7.4.

Given the temperature dependence of $W_b$ and $q_m$, Eq. (4.1) is a non linear equation which is solved using ABAQUS/STANDARD and an external user defined subroutine to introduce the temperature dependent heat generation due to the volumetric blood
Table 7.4: Cerebral blood flow variation during hyperemia for different core temperatures $T_a$.

<table>
<thead>
<tr>
<th>$T_a$ °C</th>
<th>$CBF_M/W_o$</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>242.70</td>
</tr>
<tr>
<td>35</td>
<td>194.95</td>
</tr>
<tr>
<td>37</td>
<td>187.50</td>
</tr>
<tr>
<td>42</td>
<td>187.50</td>
</tr>
</tbody>
</table>

These variations were approximated from [56, 57]. Where $W_o$ is the basal cerebral blood flow value.

perfusion and tissue heat production. The system is solved considering that the neck base in insulated, and the skin surface subjected to either natural convection, forced convection, or fixed skin temperature, as seen in Fig. 7.10a.

7.2.2 Discussion of Results

In this section, the temperature in the infarct site is calculated during and after temporary vascular occlusion using the thermal model and the temporal variations in metabolic activity and blood flow described by Eqs. (7.1)-(7.5). The calculations consider the case of external and whole body cooling during and after regional ischemia produced by cerebral stroke. The duration of the vessel occlusion, the reduction of blood flow and metabolic activity, as well as the variations of these parameters during and after stroke were approximated from several experiments reported in the literature [19, 22]. The objective of this study is to determine the effect that variations on the regional metabolic rate, regional blood flow, surface cooling and arterial temperature have on the local ischemic temperature. This study is useful in the investigation of the existence of an optimal time window for hypothermic treatment [65, 31, 70, 19].

The calculations presented in this section correspond to two different stages char-
acterized by vascular occlusion (Stage I), and reperfusion (Stage II). In each one of
these stages, cooling is performed either by surface cooling, or by arterial tempera-
ture reduction. External cooling, is achieved by either fixed skin temperature, or by
forced convection at the skin surface [44]. The values used for the convection coeffi-
cient $h$ in the case of natural convection, and external cooling by forced convection
were taken from Ref. [28], and correspond to $h = 5 \text{ W/m}^2\text{oC}$ and $h = 30 \text{ W/m}^2\text{oC}$,
respectively. Whole body cooling is achieved by varying the arterial blood tempera-
ture $T_a$ with time at different rates. Experimentally this is achieved by intravascular
catheterization[48], at a rate of $2^\circ\text{C/h}$ (rapid cooling) or $6^\circ\text{C/h}$ (ultra-rapid cooling).
Since mild to moderate hypothermia improves the outcome after ischemia produced
by temporal vessel occlusion, temperature reduction of $2^\circ\text{C}$ is considered in the cal-
culations presented herein.

The temperature distribution during Stage I is calculated using the blood flow and
metabolic activity described by Eq. (7.1), and the values of blood flow and metabolic
heat during stroke or vessel occlusion $W_{sj}$ and $q_{sj}$ defined in Eq. (7.2). The initial
temperature distribution used in the calculations during Stage I, corresponds to the
steady temperature distribution obtained for the case of insulated boundary at the
neck base, natural convection at the skin surface, and normal cerebral blood flow and
metabolism. During Stage II or reperfusion, the blood flow is varied according to Fig.
7.8 and Eqs. (7.4)-(7.5).

The results presented in this section correspond to temperature contour plots
of the infarct region on an axial plane, and to the temperature history of different
points within the stroke region, as indicated in Fig. 7.10. In this figure, the space
occupied by the infarct region is shown in gray, and the temperature observation
points ($P_1, P_2, P_3, P_4$ and $P_5$) are marked. The points $P_1$ and $P_5$ lay within
the penumbra, $P_2$ and $P_4$ fall in the boundary between penumbra and core; and $P_3$ is a
point in the center of the stroke core. Fig. 7.11, shows the temperature history of
points $P_1$ to $P_5$ during two hours of vascular occlusion (top), and the temperature
Figure 7.10: FE Mesh generated from a CT scan of an adult male. (a) The boundary conditions at the skin surface and the neck base, and an axial plane (z = 0.625 m) where the result is presented. (b) Points inside the infarct region along the axial plane chosen.

contours inside the infarct region after 41 minutes of vascular occlusion (bottom) when the regional blood flow, and the tissue metabolic heat produced by the infarct region are reduced 75% (s = 0.25) and 50% (γ = 2) respectively. During stroke, the temperature at every point increases as time progresses, it reaches a maximum and then it is reduced slightly. The temperature difference between points $P_1$ and $P_5$ is about 0.4°C, this difference is the result of the presence of the bone/brain interface closer to point $P_1$. To observe the temperature variation of the infarct region during the progression of stroke regardless of the effect of geometry, Fig. 7.12 shows the contours for the temporal temperature change $\Delta T(r) = T(r, t) - T(r, t = 0)$, where one observes that the temperature variation inside the stroke region is symmetric and has a maximum at the core.

Fig. 7.13, shows the temperature history during vessel occlusion for the points $P_1$ to $P_5$, when the rCBF is reduced 75% (s = 0.25) and 85% (s = 0.15) of the normal value, and the rCMRO$_2$ is reduced by a value equal to γs, as indicated in Eqn. 7.3, where $\gamma = 1, 2$. In this figure it is observed that the tissue temperature reaches
Figure 7.11: Temporal variations of the average temperature at the core and penumbra regions during Stage I or vascular occlusion, for the case of 75% reduction in the rCBF ($s = 0.25$) and 50% ($\gamma = 2$) reduction of the regional cerebral metabolic rate. Temperature contours inside the stroke region after 41 minutes of vascular occlusion. These results correspond to natural convection at the skin surface ($h = 5 \, W/m²\,°C$ and $T_{\infty} = 20\,°C$).
Figure 7.12: Contour lines inside that show the temperature difference $\Delta T(r, t) = T(r, t) - T(r, t = 0)$ inside the stroke region after 41 minutes of vascular occlusion for the case of 75% reduction in the regional cerebral blood flow ($s = 0.25$) and $\gamma = 2$. These results correspond to natural convection at the skin surface ($h = 5 \text{ W/m}^2\text{C}$ and $T_\infty = 20^\circ\text{C}$).

A steady distribution after two hours of vascular vessel occlusion independently of the case considered ($s$ and $\gamma$); It is also observed how variations in the reduction rate and the relationship between metabolic heat and blood flow ($\gamma$) affect the local temperature. As expected, larger reductions in blood flow and metabolism produce larger temperature drops, and that the temperature change is larger in the core region than in the penumbra site. From Fig. 7.13 one observes that the case of $\gamma = 2$ and 75% of blood flow reduction, shows the maximum observable temperature increment; consequently, all the results presented next, will correspond to the case of $\gamma = 2$ and 75% of blood flow reduction.

Figure 7.14 shows the temperature variation during and after vascular occlusion at normal temperature. The blood flow is restored after two hours of 75% vascular occlusion. In this case the temperature of the core and penumbra after 4 hours of reperfusion is less than the normal temperature of the corresponding points. Such temperature reduction results from the fact that the metabolic rate during the early
Figure 7.13: Temperature history for selected points inside the infarct region during Stage I or vascular occlusion, for the case of 75% and 85% reduction in the rCBF, and 50% ($\gamma = 2$) and 75% ($\gamma = 1$) reduction of the regional cerebral metabolic rate. These results correspond to natural convection at the skin surface ($h = 5\ W/m^2\text{°C}$ and $T_\infty = 20\text{°C}$).
Figure 7.14: Temperature history during and after vascular occlusion for the case of 75% of regional blood flow reduction and $\gamma = 2$ for the normothermic case. rCBF and rCMRO$_2$ vary according to Figs. 7.8, and 7.9, respectively. Vascular occlusion is extended for two hours and natural convection at the skin surface ($h = 5 \text{ W/m}^2\text{°C}$ and $T_\infty = 20\text{°C}$) is assumed at all times.

Stages of reperfusion is lower than the normal metabolic rate. In this case, the temperature of point $P_1$ presents the smallest variations, and $P_3$ shows the larger temperature change as expected from the percentile variations in blood flow and metabolic activity in the core region. The point $P_5$, which lays closer to the deep brain shows the larger temperature.

For the hypothermic case, cooling is produced in three different ways: surface convection, fixed external temperature, and whole body cooling. Figure 7.15(a) shows the temperature distribution after two hours of vascular occlusion and one hour of rapid whole body cooling (2°C/h) for the case of 75% reduction in regional blood flow and 50% reduction in the regional metabolic activity ($\gamma = 2$) during occlusion. The temperature change within the stroke region after cooling during vascular occlusion is about 0.5°C. It is observed that the temperature in the stroke region closer to the
bone is smaller than the temperature of points in the deep brain. Due to residual metabolic activity, the temperature at the core is higher than in the surrounding penumbra. After one hour of cooling, and once the arterial temperature has reached $35^\circ C$, reperfusion is started following the temporal variations of the blood flow and metabolism given by Eqs. (7.4)-(7.5). The temperature history of points $P_1$-$P_5$ during reperfusion after rapid whole body cooling are presented in Fig. 7.15(b), where one observes that the temperature in the ischemic region falls approximately $0.5^\circ C$ during the first 30 minutes of reperfusion and it stabilizes after 2 hours of restarting the blood flow. It is seen that the temperature in the infarction core is lower than the temperature of the surrounding healthy tissue.

On the other hand, Figs. 7.16-7.17, show the temperature variation due to surface cooling by forced convection at the skin surface, when the external cooling is started after one hour of vessel occlusion, and continued during reperfusion as indicated by the arrow in Fig. 7.16. In these figures one observes that external cooling is very effective during vessel occlusion, and that after reperfusion starts the temperature increases in the center of the core region, but the final temperature after several hours of reperfusion is about $1^\circ C$ less than the normal temperature value in each region. Fig. 7.17 show the temperature distribution after two hours of vascular occlusion and one hour of surface cooling. The temperature distribution in the stroke region is very asymmetric due to surface cooling, and there is about $1^\circ C$ temperature difference between points $P_1$ and $P_5$. When external cooling is during reperfusion or Stage II, the same temperature distribution is reached after one to two hours of cooling. Finally, for the case of external cooling by fixing the skin temperature to $10^\circ C$ the same behavior is observed, but the temperature gradients are larger than those observed for the case of surface cooling by convection due to the lower skin temperature.
Figure 7.15: Temperature variations for the case of rapid cooling at a rate of 2°C/h; 75% of blood flow reduction and 50% reduction in the regional metabolic rate (γ = 2) during Stage I. The contour plot in the top shows the temperature distribution inside the infarct region after two hours of vascular occlusion and one hour of rapid cooling. The plot in the bottom shows the temperature history of points $P_1$ to $P_5$ during reperfusion after cooling to $T_a = 35°C$ was achieved.
Figure 7.16: Temperature variations for the case surface cooling by forced convection during and after vessel occlusion. Cooling is started after one hour of stroke onset. Vascular occlusion to 75% of regional blood flow occlusion lasted two hours. Surface cooling is extended after vascular occlusion. These results correspond to $\gamma = 2$. In the case of forced convection, at the skin surface $h = 30 \, W/m^2\cdot{}^\circ{}C$ [28] and $T_{\infty} = 20\,{}^\circ{}C$.

Figure 7.17: Temperature distribution for the case surface cooling by forced convection after 2 hours of vessel occlusion and one hour of surface cooling. Cooling is started after 1 hour of 75% of regional blood flow occlusion. These results correspond to $\gamma = 2$, $h = 30 \, W/m^2\cdot{}^\circ{}C$[28] and $T_{\infty} = 20\,{}^\circ{}C$. 
7.2.3 Section Summary and Important Remarks

In the present section, a thermal model was used to determine the temperature variations in the brain tissue and infarct region during and after regional ischemia caused by stroke. This is the only study that exploits the realistic head geometry to study regional temperature changes due to local variations in blood flow and metabolic activity. Given the possible application of hypothermia in the treatment of stroke, three different cooling strategies were considered that correspond to: surface convection, fixed external temperature, and whole body cooling. With the aid of a realistic thermal model that incorporates real localized variations in the blood flow and metabolic activity that occur in the infarct region, the existence of an optimal time window for hypothermic treatment can be studied.

From the calculations it was observed that, the temperature change in the stroke region calculated during vascular occlusion in normothermic conditions is less than 0.25°C, and the value depends considerably on the reduction in the regional blood flow and the metabolic heat in the infarct region. The small temperature reduction observed in the infarct region during vascular occlusion is due to the residual metabolic heat of the ischemic tissue, and due to heat conduction from the surrounding healthy tissue. In this work experimental measurements of blood flow and metabolic activity for primates were used [19]-[22], but exact values for humans are unknown, and variations can strongly affect the temperature changes and distribution in the stroke zone. Also, the presence of inflammatory processes occurring in the infarction zone as the result of ischemia and that increase local tissue temperature should be introduced.

Surface cooling can reduce dramatically the temperature of the stroke region nearest to the skin surface and increases the temperature gradients within the stroke region. For the cases considered, the temperature reduction was 1°C and 6°C during forced convection and fixed skin temperature, respectively. It is observed that cooling is more effective when started during vascular occlusion due to the reduced blood flow and the drop in the metabolic rate caused by the temperature fall.
Chapter 8

Conclusions

Cooling brain tissue is important in the treatment of head trauma, stroke, or after birth asphyxia. We observed that independently of the external boundary condition, reducing the deep tissue temperature only by surface cooling is impossible due to the high blood flow in the brain tissue.

The ability to control the deep tissue temperature strongly depends on the temperature of the arterial blood entering the brain, which can be altered by extracorporeal perfusion. Once the arterial temperature has been lowered, variations in the physiological parameters can help to reduce or increase temperature gradients in the brain.

The model is able to reproduce the trends observed in all the experiments considered in the validation process. This study shows the importance of incorporating direct measurements of variables that heavily influence the brain temperature, such as the blood flow, the tissue oxygen consumption, and the arterial temperature. Differences between the calculated temperature values and the direct measurements are observed. These variations are associated to the uncertainty of different parameters such as the thermal conductivity, the tissue metabolism, the bone and skin blood flow, as well as the geometrical parameters.

Our calculations show that if the blood flow during DHCA is stopped far from an equilibrium temperature distribution, the tissues have not been properly cooled down and the temperature in the deep brain tissue raises due to the residual metabolic activity, canceling the beneficial effect of hypothermia.

Contrary to previous observations during normothermia, the simulations performed show that external cooling has a considerable effect during ischemia, and
can be used to better control the brain temperature during CA. The calculations during circulatory arrest shown that when the external skin temperature is set at a temperature close to the target cooling temperature, the temperature gradients during the circulatory arrest are reduced, and the deep brain temperature decreases with time, helping to reduce the residual cerebral metabolism and ensuring the protective effect of hypothermia. From the calculations during circulatory arrest, it was also observed that the cooling time for children doubles that of adults due to reduced blood flow and increased metabolism.

The temperature change in the stroke region calculated during vascular occlusion in normothermic conditions is less than 0.25°C, and the value depends considerably on the reduction in the regional blood flow and the metabolic heat in the infarct region. The small temperature reduction observed in the infarct region during vascular occlusion is due to the residual metabolic heat of the ischemic tissue, and due to heat conduction from the surrounding healthy tissue.

It was observed that surface cooling during vascular occlusion can reduce dramatically the temperature of the stroke region nearest to the skin surface and increases the temperature gradients within the stroke region. As in the case of global ischemia, it is observed that cooling of the infarct region is achieved faster when started during vascular occlusion.

The model validation using swine measurements helped us to realize the importance of the geometry and tissue layer thickness, this directed us to develop a realistic 3D-model obtained from tomographic data. Results using the realistic model show the same behavior that those of the layered model, but the nonspherical shape of the head and the local variation of the tissue thicknesses has an important effect in the temperature distribution. The realistic model also allowed us to perform calculations involving focal ischemia, which can greatly improve cooling therapies.
Chapter 9

Future Work

To keep improving the thermal model developed during this research project, a non-linear physiological model that considers the relations between blood flow, gas dynamics and tissue oxygen delivery can be coupled with the thermal model[47]. This new model will allow to study the factors that limit the success of hypothermia and to explain why sometimes hypothermia has a negative effect in the setting of hypoxia and ischemia.

To study the effect of hypothermia in the tissue oxygen transport and blood flow, the effect of temperature on factors such as the plasma viscosity, the oxygen affinity of blood, the oxygen diffusion, as well as the vessel resistance and compliance need to be introduced in the thermal model. The dynamics of the cerebral blood perfusion together with the effect that temperature has over the gas exchange and autoregulation, will allow us to analyze the effect of temperature over the system stability. The proposed research will be applicable in the optimization of experiments and therapies involving deep hypothermic circulatory arrest, or in the treatment of hypoxia-ischemia resulting from asphyxia, or brain injury. Ultimately, this research will help clinicians to design experiments and reduce animal experimentation by relaying in validated mathematical models. The activities proposed for the study of cooling and rewarming strategies maximizing oxygen delivery are as follows:

1. Implement a compartmental model of oxygen transport similar to that of Sharan et al[72], and introduce the temperature dependence in factors such as: the oxyhemoglobin dissociation curve, the metabolic rate of oxygen consumption, the cerebral blood flow and the oxygen diffusivity.
2. Study the temporal variation of the oxygen diffusion and absorption using reported measurements of blood flow, temperature and metabolic rate. These calculations will show the time response of oxygen transport, and will help determine if oxygen delivery matches the tissue oxygen requirements during hypothermic therapies.

3. The temperature dependence on the arterial vascular resistance and compliance, the metabolic rate of oxygen and the gas diffusion constants will be introduced in the integrated cardiopulmonary (CP) model of Lu et al [47], which considers cerebral autoregulation and gas exchange.

4. Couple the integrated CP model with the thermal model and perform calculations for hypothermia during hypoxia, ischemia and cardiopulmonary bypass. The lumped brain temperature $T_i$ is used due to the compartmental nature of the hemodynamic and oxygen exchange models.

Appendix D presents some preliminary results regarding the effect of temperature on the oxygen transport which validate the importance of the proposed future research.

Another important part in the improvement of the thermal model discussed here is the consideration of the temperature variation of thermophysical properties such as the tissue thermal conductivity. Also, the thermal effect of macrovessels in the system, as well as the countercurrent heat transfer of neck vessels should be included for more accurate temperature predictions. In the same direction, introduction and characterization or more tissue types is necessary to achieve the afore mentioned goal. Finally, refinement of the cooling boundary conditions and determination of the localized convection coefficient $h$ is necessary for accurate thermal modeling.
Appendix A

Heat Transfer in Thermally Significant Blood Vessels

Thermally significant blood vessels correspond to arteries and veins of diameters between $5000\mu m$ and $300\mu m$, which are not in thermal equilibrium with the surrounding tissue due to the high velocity of the blood that they transport. Because of their size and length, these vessels are referred as macrovasculature and in a tissue they form the basic structures shown in Fig. 2.3, that correspond to: a single vessel buried in a tissue, a countercurrent pair, and a single vessel near a surface.

The study of heat transfer systems containing a collection of vessels or pipes with the geometries observed in Fig. 2.3, began because their various industrial applications like power plant steam and water distribution lines, heat exchanger design, buried pipes and solar collectors. During the 1980’s, due to the interest in local hyperthermia studies for cancer treatment, the need to estimate the thermal effects of blood flow arose. Since then, several authors have studied heat transfer in these major vessel structures ([12]-[97]); In Table A, we have summarized these contributions. In these studies, we find approximate and exact solutions; these last are based in conformal mapping techniques using cylindrical or bicylindrical coordinates in the case of countercurrent pairs. The approximate solutions, instead, are based on superposition of infinite line heat and sink source solutions for vessels located in the center of a cylinder, or use perturbed solutions for cases of small eccentricity.

One of the most recent papers dealing with the heat transfer of blood vessels embedded in a tissue was written by Zhu, Weibaum and Jiji [97]. This paper presents an approximate analytic solution to determine the heat exchange between several
axially interacting vessels eccentrically embedded in a tissue cylinder subject to surface convection. The solution is constructed by superposition of an approximate non-conformal solution which satisfies the boundary conditions exactly only when the thermal conductivity of the fluid ($k_f$) is equal to that of the tissue ($k_t$), i.e. $\bar{k} = \frac{k_f}{k_t} = 1$. For a single vessel, and a system where $\bar{k} \approx 1$, the error associated to the approximate solution is of the order of 1%, and the error associated to the multi-vessel solution is expected to be of the same order of magnitude. This approximate solution method is very useful when dealing with blood vessels and tissue, because $\bar{k} < 1$. 
Table A.1: Studies in Countercurrent Heat Exchange

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Description, Boundary Conditions and Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chato [12]</td>
<td>Single vessel in a infinite medium, two unequal vessels at uniform surface temperature embedded in an infinite medium, and a single vessel in a semi-infinite medium with convection at the surface.</td>
</tr>
<tr>
<td>Bau and Sadhal [4]</td>
<td>Single vessel in a infinite medium with constant temperature at the surface.</td>
</tr>
<tr>
<td>Wissler [90]</td>
<td>Steady state temperature field produced by a countercurrent pair in a infinite medium. Linear temperature distribution in the z direction. Continuity of temperature and heat flux at the surface of the vessels.</td>
</tr>
<tr>
<td>DiFelice and Bau [21]</td>
<td>Eccentric annulus, buried pipe, and two cylinders in an infinite medium. Convective boundary conditions are imposed. Using bicylindrical coordinates and conformal mapping, an exact solution is obtained. An approximate solution (5 % accurate) for the geometric shape factor is obtained.</td>
</tr>
<tr>
<td>Baish et al [3]</td>
<td>Two vessels symmetrically placed in a cylinder. Constant temperature at the tissue surface, and third kind boundary conditions at the vessel walls. The heat conduction into the countercurrent vessels is determine by the difference between $T_a$ and $T_v$, and $T_i$ and the average tissue temperature $(T_a + t_v)/2$.</td>
</tr>
</tbody>
</table>
Table A.1: Studies in Countercurrent Heat Exchange (Continuation)

<table>
<thead>
<tr>
<th>Model</th>
<th>Model Description, Boundary Conditions and Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Countercurrent vessel pair asymmetrically embedded in a cylinder with surface convection.</td>
</tr>
<tr>
<td>Zhu et al</td>
<td>Continuity of $T$ and $q$ on the vessel walls.</td>
</tr>
<tr>
<td>[96]</td>
<td>Heat loss from the vessels to the surrounding tissue is small compared to the heat exchange between vessels.</td>
</tr>
<tr>
<td></td>
<td>A perturbation method is used and the 0th order solution is determined.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Considers the system of Zhu et al [96], but it is extended to arbitrary eccentricity</td>
</tr>
<tr>
<td>Zhu et al</td>
<td>A new approximate (non-conformal mapping) solution to the single vessel with arbitrary eccentricity is obtained,</td>
</tr>
<tr>
<td>[97]</td>
<td>and a solution to the multiple embedded vessel problem is obtained by superposition.</td>
</tr>
</tbody>
</table>
Appendix B

Swine Measurements used for the Model Validation

The experiments presented in this section and used in Chapter 6 are part of a series of studies to examine brain temperature as a determinant of brain injury [36], and were performed by Dr. Laptook and his collaborators at the Department of Pediatrics, of the University of Texas Southwestern Medical Center. These results are unpublished at present [36].

Mini-swine of two different ages (newborn, age 5±3 days, x±sd, n=8; older, age 34±5 days, n=10) were studied after tracheotomy, initiation of mechanical ventilation, and placement of appropriate catheters and temperature probes. The Institutional Animal Care and Research Advisory Committee of the University of Texas, Southwestern Medical Center, approved the animal instrumentation and experiments. Temperatures were monitored from 5 different sites in each animal; thermocouple microprobes were positioned at 2 cm and 1 cm beneath the parietal cortical surface (via burr holes in the cranium), on the overlying dura and skin, and in the rectum. Measurements were acquired during 3 different conditions; control, ischemia, and following ischemia.

Brain ischemia was achieved by combining hemorrhagic hypotension with inflation of a blood pressure cuff positioned around the neck to impede venous return. Rectal temperature was maintained normothermic, and the $O_2$ and $CO_2$ tension were maintained normoxic and normocapnic throughout the study. Cerebral blood flow (CBF) was measured with fluorescent microspheres and was used to derive cerebral oxygen uptake ($CMRO_2$). CBF was measured in duplicate during control and ischemia to
Table B.1: Cerebral blood flow and metabolic rate of oxygen consumption measured during ischemia experiments

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischemia</th>
<th>Post-Ischemia</th>
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</thead>
<tbody>
<tr>
<td><strong>CBF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>50 ± 20</td>
<td>17 ± 15</td>
<td>40 ± 21</td>
</tr>
<tr>
<td>Older</td>
<td>66 ± 20</td>
<td>21 ± 17</td>
<td>41 ± 19</td>
</tr>
<tr>
<td><strong>CMRO&lt;sub&gt;2&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborn</td>
<td>2.7 ± 1.0</td>
<td>1.4 ± 1.1</td>
<td>2.8 ± 1.4</td>
</tr>
<tr>
<td>Older</td>
<td>3.4 ± 1.0</td>
<td>1.7 ± 1.0</td>
<td>2.7 ± 0.8</td>
</tr>
</tbody>
</table>

verify steady state conditions.

**Results**

CBF/CMRO<sub>2</sub>: Values for CBF and the associated derived CMRO<sub>2</sub> during control, ischemia and following ischemia are listed in the table. Values during control and ischemia were performed in duplicate to assure a constant blood flow during these intervals and were averaged since the replicates were similar. Ischemia was characterized by a dramatic fall in CBF, and there was partial recovery of CBF during the post-ischemia interval. Parallel changes were present for CMRO<sub>2</sub>.

Temperatures: The temperatures of the newborn and older swine brain at multiple sites and the rectum are plotted over time in Figs. B.1 and B.2. In each group ischemia was associated with a reduction in brain temperature. The fall in temperature was greatest for the thermocouples placed closer to the brain surface i.e., overlying dura > 1 cm depth > 2 cm depth. These changes were present in both age groups but the extent of change was larger for the younger animals.
Figure B.1: Experimental temperature history for various depths, for newborn swine [36]. The vertical broken lines indicate the interval of brain ischemia.

Figure B.2: Experimental temperature history for various depths, for one month old (b) swine [36]. The vertical broken lines indicate the interval of brain ischemia.
Appendix C

Glossary & Acronyms

C.1 Glossary of Terms

Asphyxia: Impairment of gas exchange that is caused by altered ventilation. Cases of severe asphyxia can result in hypoxia and hypercapnia.

Circulatory Arrest: Condition where blood flow circulation is stopped.

Homeotherm: Organism capable of maintaining its core temperature within a specific temperature range.

Hyperthermia: Case where the core temperature is above its normal range.

Hypothermia: Subnormal body temperature.

Hypoxia: Condition where the oxygen level of a tissue are below the normal value. It can be produced by lack of blood flow, anemia, or respiration of air with low concentration of oxygen.

Hypoxia-Ischemia: Condition caused by reduction in blood flow together with reduction in tissue oxygen content.

Ischemia: Suppression of blood flow in an organ or tissue that creates local anemia or hypoxia.

Segmentation: Process through which objects are separated or distinguished from background. For intensity images (ie, those represented by point-wise intensity levels) four common approaches are: threshold techniques, edge-based methods, region-based techniques, and connectivity-preserving relaxation methods.

Selective head cooling: Cooling strategy where the head is cooling by contact with ice packs or cooling blankets, and the arterial or core temperature is kept at a constant value close to the normal core temperature.
**Stroke:** Cerebrovascular accident where blood flow is interrupted in a region of the organ, mainly heart and brain. Strokes are caused either by occlusion of cerebral blood vessels leading to ischemic necrosis of the brain (cerebral infarction) or by rupture of blood vessels resulting in hemorrhage in the brain or in the subarachnoid space (intracranial hemorrhage). Vascular occlusion: Interruption of blood flow in a major artery that can be permanent or last a few hours.

**Whole body cooling:** Reduction of the core temperature using techniques such as hypothermic cardiopulmonary bypass, or covering the whole body with cooling blankets.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>Arterial blood pressure</td>
</tr>
<tr>
<td>BI</td>
<td>Brain injury</td>
</tr>
<tr>
<td>CA</td>
<td>Circulatory arrest</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
</tr>
<tr>
<td>$CMRO_2$</td>
<td>Cerebral metabolic rate of oxygen consumption</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CP</td>
<td>Cardiopulmonary</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVR</td>
<td>Cerebrovascular resistance</td>
</tr>
<tr>
<td>ICD</td>
<td>Intracranial dynamics</td>
</tr>
<tr>
<td>MABP</td>
<td>Mean arterial blood pressure</td>
</tr>
<tr>
<td>MR</td>
<td>Metabolic rate</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>ODC</td>
<td>Oxygen dissociation curve</td>
</tr>
<tr>
<td>PP</td>
<td>Perfusion pressure</td>
</tr>
<tr>
<td>SHC</td>
<td>Selective head cooling</td>
</tr>
<tr>
<td>WBC</td>
<td>Whole body cooling</td>
</tr>
</tbody>
</table>
Appendix D

The Effect of Hypothermia on the Oxygen Delivery to Cerebral Tissue: A Compartmental Model

D.1 Introduction

This work was done as preliminary analysis in the study of factors that affect the success of hypothermic therapies. Hypothermia has important clinical applications because it limits the extent of brain injury by reducing the oxygen and glucose uptake, allowing the tissue to sustain prolonged periods of oxygen deprivation. Most evidence suggests that hypothermia provides remarkable protection during hypoxia and ischemia. However, some of the studies involving the use of hypothermia have shown contradictory results or have not improved the outcome as expected. A possible explanation of the failing of hypothermic therapy is that attention to the coupling between cerebral blood and metabolism and the effect of temperature in the oxygen dissociation curve have been neglected.

Oxygen is carried in the blood by hemoglobin and it can also be found dissolved in the plasma. Oxygen transport between blood and brain cells depends on factors like the cerebral blood flow (CBF), the oxygen affinity of the blood ($P_{50}$), the hematocrit (H), the tissue oxygen consumption ($CMRO_2$), and the concentration of oxygen in the arterial blood ($PaO_2$). The oxygen delivery and absorption to and by the tissue can be described by mathematical models of microcirculation, which are classified in two major types: those that consider vessel geometry and distribution, and into compartmental models. A complete description of these models and the theory of oxygen transport in tissues is presented by A. Popel in Ref. [66].
In this section a compartmental model of oxygen transport, similar to that of Sharan [72], is implemented and the temperature dependence in factors such as: the oxyhemoglobin dissociation curve (ODC), the metabolic rate of oxygen consumption \((CMRO_2)\), the cerebral blood flow \((Q)\) and the oxygen difussivity \((D^T)\) are introduced. Then, the temporal variation of the oxygen concentration in the different compartments is calculated using reported measurements of blood flow, brain temperature and metabolic rate. The calculations presented herein show the steady state distribution of oxygen for different tissue temperatures, and the temporal variations on the tissue oxygen levels during two cooling modalities. Also, the effect of temperature during hypoxia is studied.

The compartmental model presented here is used to determine the oxygen concentration in the cerebral tissue given tissue temperature variations and variations in the oxygen content of the blood entering the brain. The present study can be used to determine the effect of hypothermic therapies on the oxygen delivery and tissue oxygen utilization of the cerebral tissue, which are factors known to limit the success of hypothermia.

### D.2 Compartmental Model of Tissue Oxygen Transport

In a compartmental model, the vascular bed and the corresponding tissue are modeled as a series of compartments: \(m\) arteriolar compartments, \(m\) venular compartments, a capillary compartment and a tissue compartment. As blood flows through the vascular bed, the oxygen is transported by convection to the next vascular compartment, and by diffusion to the surrounding tissue where it is utilized. Fig. D.1 shows the compartmental model of oxygen transport; in this diagram, the subindices \(a, c, v\) and \(t\), are used to denote the arteriolar, capillary, venular and tissue compartments, respectively. \(Q\) corresponds to the cerebral blood flow, \(D^T\) represents the oxygen diffusion conductance of each compartment, and \(M\) is the tissue oxygen consumption rate \((CMRO_2)\). \(p\) is the oxygen tension or \(PO_2\) at the inlet/outlet of each compart-
Figure D.1: Compartmental model of oxygen transport in the cerebral microcirculation. The subindices $a$, $c$, $v$ and $t$, represent the arteriolar, capillary, venular and tissue compartments. $Q$ denotes the cerebral blood flow, $P_i$ represents the average pressure of the vascular compartment, $p_i$ is the oxygen pressure at the inlet or outlet of each compartment, $D_i^T$ is the gas diffusion conductance between the vessel compartment and tissue; $C_i$ denotes the compartmental oxygen content, $V_i$ represents the compartment volume, and $M$ is the rate of cerebral oxygen consumption.

\begin{align}
    P_i &= \frac{(p_{i-1} + p_i)}{2}, \\
    P_c &= (1.2838 - 0.09513 \ln(p_{am})) \frac{(p_{am} + p_{vm})}{2}
\end{align}

for the vessel and the capillary compartments, respectively.

Imposing mass balance at the vascular and at the tissue compartments, the following system of equations is obtained for the oxygen concentration $C_i$ and partial pressure of oxygen $p_i$ in each compartment:

\begin{align}
    \frac{dV_{ai} \dot{C}_{ai}}{dt} &= Q \left(C_{a(i-1)} - C_{ai}\right) - D_{ai}^T (P_{ai} - P_{i}), \\
    \frac{dV_c \dot{C}_c}{dt} &= Q \left(C_{am} - C_{vm}\right) - D_c^T (P_c - P_{i}) \\
    \frac{dV_{vi} \dot{C}_{vi}}{dt} &= Q \left(C_{vi} - C_{v(i-1)}\right) - D_{vi}^T (P_{ai} - P_{i})
\end{align}
\[
\frac{dV_i C_i}{dt} = \sum_{i=1,j=a,v}^{m} D_{ai}^T (P_{ai} - P_t) + D_c (P_c - P_t) - MV_t, \tag{D.2d}
\]

for \( i = 1, 2, \ldots, m \), and \( j = a, v \). In the previous set of equations, \( V_i \) is the volume of each compartment, and \( C_i \) represents the oxygen content in the blood at the outlet of the \( ith \) compartment. \( \bar{C}_i \) corresponds to the average oxygen content in each compartment and it is defined by

\[
\bar{C}_i = \begin{cases} 
(C_{i-1} + C_{i+1})/2, & \text{for the vessel compartments} \\
\alpha_i P_t, & \text{for the tissue compartment}
\end{cases} \tag{D.3}
\]

where \( \alpha_t \) is the solubility of oxygen in the tissue. The oxygen concentration in each compartment \( C_i \) is expressed as

\[
C_i = \alpha p_i + \beta HS(p_i, T), \quad i = 1, \ldots, m. \tag{D.4}
\]

In the previous equation, \( \alpha \) represents the solubility of oxygen in blood, \( \beta \) is the oxygen carrying capacity of blood, \( H \) is the blood hematocrit, and \( S \) is the oxyhemoglobin dissociation curve (ODC). The oxygen carrying capacity of blood \( \beta \) is defined as

\[
\beta = 1.34 Hb (1 - SCO)/H^\circ, \tag{D.5}
\]

where \( Hb \) is the total hemoglobin concentration in g/100 ml of blood, \( H^\circ \) is the blood hematocrit at normal conditions, and \( SCO \) is the fractional saturation of hemoglobin with \( CO_2 \). For sheep, \( Hb = 0.11 \) g/100 ml of blood, \( H^\circ = 0.3 \) (i.e. 30\% saturation), and in the calculations, \( SCO \) is assumed to be equal to zero.

The ODC describes the binding of oxygen with hemoglobin and shows the equilibrium of oxyhemoglobin and nonbonded hemoglobin at various partial pressures of oxygen \( (PaO_2) \) and has a sigmoid shape due to the cooperative binding of the hemoglobin. The ODC varies with temperature, among other parameters, and such variations will be discussed the latter on. Finally, the values of \( p_{ao} \) and \( C_{ao} \) correspond to \( PaO_2 \) and \( CaO_2 \), which can be measured directly.

In the compartmental model shown in Fig. D.1 and described by Eq. (D.2) oxygen is transported by convection among the different compartments and it is also diffused
to the tissue due to variations in the oxygen partial pressure between the vascular and the tissue compartments. In other compartmental models of oxygen transport [71], oxygen diffusion due to countercurrent transport of oxygen between paired vessels is considered; however, oxygen transport between coupled artery-vein is not observed in the cerebral vasculature, and in this work will not be considered.

**D.3 Temperature Dependent Oxygen Transport**

It has been mentioned before that oxygen transport depends on parameters such as CBF, tissue metabolic activity and the oxygen affinity of blood; in this section, the effect that temperature has on such parameters is presented. The tissue oxygen consumption $CMRO_2$ or metabolic rate is observed to depend exponentially on the temperature, following the $Q_{10}$ law [73]. Assuming first order kinetics [66], the tissue oxygen consumption is set proportional to the the tissue oxygen concentration $P_t$. The relation for the cerebral metabolic rate of oxygen consumption is expressed by

$$CMRO_2(T) = \frac{CMRO_2^o}{P_t^o} Q_{10}^{(T-T_a)/10} P_t,$$

where $CMRO_2^o$ and $P_t^o$ correspond to the cerebral metabolic rate of oxygen consumption and average tissue oxygen concentration under basal conditions; $Q_{10}$ represents the van’t Hoff temperature coefficient, which varies with the species and age; $T$ is the average tissue temperature, and $T_a$ the arterial blood temperature entering the tissue. Experiments have shown [6] that, the oxygen diffusion coefficients $D^T$ show the same temperature dependence as the cerebral metabolic rate of Eq. D.6.

The cerebral blood flow is another important parameter in the modeling of oxygen transport and heat transfer. It is known that the blood flow in the brain is regulated by mechanisms which aim to ensure organ function that act by changing the vascular resistance of the arterial bed, and that such mechanisms exist to ensure and sustain organ function.

The oxygen dissociation curve (ODC) depends on factors like pH, temperature,
Figure D.2: Oxygen Dissociation Curve for different temperatures, using the relation proposed by Kelman [30]

The partial pressure of $CO_2$, carbon monoxide and concentration of organic phosphates; it can be expressed, among others, by the Hill equation

$$S(PaO_2) = \frac{(PaO_2/P_{50})^n}{1 + (PaO_2/P_{50})^n}$$  \hspace{1cm} (D.7)

where $n$ is known as the Hill exponent, and $P_{50}$, corresponds to the pressure at which the hemoglobin is fifty percent saturated with oxygen. $P_{50}$ represents the affinity of the hemoglobin to oxygen; when the ODC is shifted to the right or the $P_{50}$ increases, the affinity of the hemoglobin for oxygen decreases, in such case, the $O_2$ is released more easily as blood passes through the capillaries. To study the protective effects of hypothermia, the relation proposed by Kelman [30] will be considered herein. This relation incorporates the effects of pH, temperature and $PaCO_2$ in the ODC. The ODC proposed by Kelman [30] is presented in Fig. D.2 for various temperatures. As noted in Fig. D.2, the affinity of hemoglobin for oxygen ($P_{50}$) is increased as the temperature is reduced, as a result, oxygen delivery should be impeded during hypothermia. From the work of Kelman [30], the effect of temperature on the $P_{50}$
can be expressed as

\[ P_{50} = aP_{50}^o \exp(bT). \]  

(D.8)

The values of \( n, P_{50}^o, a \) and \( b \) vary among species; for sheep, \( n = 3.0, P_{50}^o = 40.74 \) mmHg, \( a = 0.1313 \), and \( b = 0.0551 \) \(^{1/{\circ}C}\).

### D.4 Appendix Results

The aim of this work is to understand the effects of tissue temperature variations on the oxygen uptake, and to determine safe temperature limits for hypothermic treatment such that the oxygen delivered to tissue is maximized. To achieve this goal, a compartmental model is used and steady state and transient calculations of the oxygen concentration in the various vascular and tissue compartments are performed for temperature variations during two different cooling strategies and during hypoxia. This study introduces the effect that temperature has on: the tissue metabolic activity, the oxygen diffusion conductance, the affinity of the blood for oxygen, \( (P_{50}) \), and the cerebral blood flow.

The average normal value for the gas diffusion conductance coefficients \( D^T \), as well as the vessel parameters used in the calculations are presented in Tables D.1 and D.2, respectively. Other parameters used in the compartmental model are the solubility of oxygen in blood \( \alpha \), the blood hematocrit \( H \), and the oxygen carrying capacity of blood, which for sheep have the magnitude: \( \alpha = 3 \times 10^{-5} \, \text{O}_2/\text{ml/mmHg} \), and \( H = 0.3 \). These parameters correspond to sheep, and are taken from [71]. For the sheep, brain has an average weight of 75 g, the head radius is about 6 cm, the normal average cerebral blood flow is 70 ml/100 g/min; finally, the basal metabolic heat released by the tissue is proportional to the \( CMRO_2 \) and has a magnitude of 17,600 \( W/m^3 \).
Table D.1: Gas diffusion conductance between tissue and cerebral arteries, veins and capillaries in the sheep [71]

<table>
<thead>
<tr>
<th>Vessel</th>
<th>$D_a^T$</th>
<th>$D_v^T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$0.22 \times 10^{-5}$</td>
<td>$0.31 \times 10^{-5}$</td>
</tr>
<tr>
<td>2</td>
<td>$0.55 \times 10^{-5}$</td>
<td>$0.76 \times 10^{-5}$</td>
</tr>
<tr>
<td>3</td>
<td>$0.20 \times 10^{-4}$</td>
<td>$0.25 \times 10^{-4}$</td>
</tr>
<tr>
<td>4</td>
<td>$0.39 \times 10^{-4}$</td>
<td>$0.47 \times 10^{-4}$</td>
</tr>
<tr>
<td>5</td>
<td>$1.20 \times 10^{-5}$</td>
<td>$1.36 \times 10^{-5}$</td>
</tr>
<tr>
<td>Capillaries</td>
<td>$0.66 \times 10^{-2}$</td>
<td></td>
</tr>
</tbody>
</table>

$D^T$ is measured in: ml O$_2$/ s/ mmHg

Table D.2: Vessel Parameters for the cerebral vessels in the sheep [71]

<table>
<thead>
<tr>
<th>Arterioles</th>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
<th>No. vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_1$</td>
<td>0.12</td>
<td>5.39</td>
<td>1880</td>
</tr>
<tr>
<td>$a_2$</td>
<td>0.06</td>
<td>2.69</td>
<td>$1.5 \times 10^4$</td>
</tr>
<tr>
<td>$a_3$</td>
<td>0.03</td>
<td>1.35</td>
<td>$1.15 \times 10^5$</td>
</tr>
<tr>
<td>$a_4$</td>
<td>0.02</td>
<td>0.9</td>
<td>$3.92 \times 10^5$</td>
</tr>
<tr>
<td>$a_5$</td>
<td>0.01</td>
<td>0.45</td>
<td>$3.01 \times 10^6$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Venules</th>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
<th>No. vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v_1$</td>
<td>0.018</td>
<td>5.39</td>
<td>1880</td>
</tr>
<tr>
<td>$v_2$</td>
<td>0.09</td>
<td>2.69</td>
<td>$1.5 \times 10^4$</td>
</tr>
<tr>
<td>$v_3$</td>
<td>0.045</td>
<td>1.35</td>
<td>$1.15 \times 10^5$</td>
</tr>
<tr>
<td>$v_4$</td>
<td>0.03</td>
<td>0.9</td>
<td>$3.92 \times 10^5$</td>
</tr>
<tr>
<td>$v_5$</td>
<td>0.015</td>
<td>0.45</td>
<td>$3.01 \times 10^6$</td>
</tr>
</tbody>
</table>
D.4.1 Steady State Calculations

We calculated the steady state oxygen distribution in the vascular and tissue compartments for different temperatures using the compartmental oxygen transport model described in Fig. D.1, and Eq. (D.2), together with the temperature dependent $P_{50}$, the tissue metabolic activity, and the oxygen diffusion coefficients. For the steady state, the system of equations (D.2) forms a nonlinear system of algebraic equations for $2m + 2$ unknowns that correspond to: $p_{ai}$ for $i = 1, \ldots, m$, $p_{vi}$ for $i = 0, 1, \ldots, m$, and $P_t$, and can be solved using the Newton-Rapson method. For the calculations, we considered temperature variations on the blood flow $Q$ following the $Q_{10}$ law, expressed by equation (D.6).

The calculated oxygen pressure in each vascular compartment ($p_i$) and the tissue compartment ($P_t$) are presented in Figs. D.3 and D.4 for the case of normoxia or normal oxygen levels at the arterial blood entering the tissue ($pa_o = 95 \text{ mmHg}$), and hypoxia ($pa_o = 60 \text{ mmHg}$), respectively. In these plots the horizontal axis represent each one of the compartments: arterial, capillary, venous and tissue. The calculations show that most of the oxygen absorption occurs at the capillary compartment.

In Fig. D.3, it is observed that as temperature falls, the partial pressure of oxygen in each compartment is reduced, and that the variation in the oxygen content for the case of hypothermia at 35 °C is very small. The small effect on the oxygen delivery to tissue observed at 35°C explains the experimental observation that 35°C is the optimal hypothermic temperature in the treatment of BI [78]. The results of Fig. D.3 show the importance of knowing the CBF and metabolic activity and their variations with temperature in the determination of the compartmental oxygen transport.

Fig. D.4, shows the variation in the compartmental oxygen tension in the case of hypoxia. In this case it is observed that the oxygen tension at the tissue compartment ($P_t$) is always less than the partial pressure of oxygen at the venous compartments ($p_{vi}$); whereas in the normoxic case, $P_t$, and $p_{vi}$ are very close to each other in value. In the hypoxic case, the distribution of oxygen observed for a temperature of 30°C
Figure D.3: Distribution of oxygen partial pressures \( (p_i) \) in the vascular network and tissue compartment \( (P_i) \) for four different temperatures. The curves are calculated using the temperature dependent \( P_{50} \) given by the Hill equation (D.7), and equation (D.8).

is very similar to that calculated for \( T = 35^\circ C \), and contrary to the normoxic case, the values of \( P_c, pv_i \) and \( P_i \) for the case of normal temperature are below the values calculated at \( T = 30 \) and \( 35^\circ C \). These results indicate that the temperature is an important parameter in the oxygen transport and can be used to control oxygen delivery to tissue.

**D.4.2 Transient Calculations**

The oxygen transport model described by Eqs. D.2, can be solved when the time variations of blood flow, metabolic activity and brain temperature are known. In the present study, the time variations of the cerebral blood flow and the tissue metabolic activity observed during different hypothermic therapies are taken from the literature [38], and the average brain temperature is calculated using a thermal model [40]-[41] that incorporates measurements of blood flow and metabolic activity, as well as the
Figure D.4: Distribution of oxygen partial pressures ($p_i$) in the vascular network and tissue compartment ($P_i$) for four different temperatures, for the case of hypoxia $p_{ao} = 60 mmHg$.

appropriate geometric parameters and thermophysical properties for sheep.

The cooling techniques followed during the experiments correspond to selective head cooling and whole body cooling. Selective head cooling is achieved by external cooling of the head by varying the skin temperature using cooling pads around the head and maintaining the body temperature constant. On the other hand, during whole body cooling, the core or body temperature is varied with time.

The percentile blood flow variations during hypothermic therapies were taken from the literature [38], and are shown in Table D.3. During these experiments it was observed that the cerebral blood flow CBF and the rate of oxygen consumption $CMRO_2$ are coupled and follow a relation of the form

$$\%CMRO_2 = \gamma \cdot (\%CBF) + \xi,$$  \hspace{1cm} (D.9)

where $\gamma$ and $\xi$ vary depending on the cooling strategy followed as shown in Table D.3. The coupling between CBF and metabolic rate observed during cooling experiments agrees with other experimental observations [73]. In Table D.3, one observes that CBF
Table D.3: Percentile blood flow (%CBF) variations during selective head cooling (SHC) and whole body cooling (WBC) taken from [38].

<table>
<thead>
<tr>
<th>time</th>
<th>SHC(^1)</th>
<th>WBC(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>30 min</td>
<td>42.66</td>
<td>57.89</td>
</tr>
<tr>
<td>120 min</td>
<td>42.66</td>
<td>57.89</td>
</tr>
<tr>
<td>140 min*</td>
<td>124</td>
<td>157.89</td>
</tr>
</tbody>
</table>

\(^1\) For SHC, \(\gamma \) and \(\xi\) in Eq. D.9 are: \(\gamma = 0.0519\) and \(\xi = -0.0024\).

\(^2\) For WBC, \(\gamma \) and \(\xi\) in Eq. D.9 are: \(\gamma = 0.0404\) and \(\xi = -0.0054\).

* Cooling during hypoxia, were \(PaO_2\) drops 82%.

is reduced during cooling and such reduction is larger in the case of selective head cooling; also, it is observed that the occurrence of hypoxia during cooling produces an increase in the blood flow to the brain.

The temperature distribution in the sheep is calculated using a geometrically simplified thermal model described in [40]. For the temperature calculation, the head is approximated by a sphere of 6 cm in radius and the time variations of the CBF and metabolic activity observed experimentally and given in Table D.3 are used. Figure D.5 shows the lumped temperature \(T_l\) calculated for the two different cooling strategies that correspond to selective head cooling (SHC) and whole body cooling (WBC), respectively. \(T_l\) is used to obtain an average brain tissue temperature than can be introduced in the compartmental model. The lumped brain temperature \(T_l(t)\) is defined as

\[
T_l(t) = \frac{\int_0^R 4\pi T(r, t)r^2 dr}{4\pi R^3/3},
\]

where \(R\) is the radius of the sphere used to approximate the head, \(r\) the radial position, and \(T\) the local tissue temperature. Fig. D.5 represents the temperature
Figure D.5: Lumped temperature variations during selective head cooling (solid line) and whole body cooling (dashed line) for the sheep. The calculations use the same time variations in the blood flow and the linear coupling between CBF and metabolic rate described in Table D.3. During the last 20 minutes hypoxia is considered by variations in $PaO_2$ at a rate of 5.35 mmHg/min.

history during 140 minutes of cooling; during the last 20 minutes of cooling, hypoxia is introduced by variations in $PaO_2$ or $pa_o$ at a rate of 5.35 mmHg/min. A detailed description the temperature calculations, is presented in [45]. As seen in Fig. D.5, lower temperatures are achieved using WBC, but selective head cooling (SHC) produces faster cooling during the first 15 minutes.

To find the time variation of the partial pressure of oxygen in the different vascular ($p_i$) and tissue compartments ($P_t$) of Fig. D.1, the system of equations (D.2) is solved using Runge-Kutta with variable step, and the time variations in the CBF, metabolic rate and tissue temperature described before (Table D.3) are used. In the calculations presented below, it is assumed that the compartmental volumes $V_i$ are constant in time. The results of the transient calculations are presented in Figs. D.6 and D.7 where time variations on the capillary and tissue oxygen tension ($P_e$ and $P_t$) for
Figure D.6: Average oxygen pressure on the capillary (solid line) and tissue (dashed line) compartments during selective head cooling (SHC - solid line) and whole body cooling (WBC - dashed line).

SHC (solid lines) and WBC (dashed lines) are shown during normoxia and hypoxia, respectively.

Comparing Figs. D.5 and D.6 one observes that the temperature, tissue and capillary oxygen pressure achieve a stationary distribution at the same time. During cooling at normal $PaO_2$ (Fig. D.6), the oxygen pressure at the capillary compartment is greater for the case of WBC. The variation in $P_t$ is very small in both cooling methodologies, and it is observed that $P_t$ increases with time for the case of selective head cooling. During hypoxic cooling, the oxygen pressure at the capillary compartment increases with time, and the increment varies little with the cooling strategy followed; $P_t$ falls, just as observed in the steady state calculations for the hypoxic case, it is also observed that the reduction in the tissue oxygen pressure during hypoxia is larger for the WBC case due to larger temperature reduction.
Figure D.7: Average oxygen pressure on the capillary (solid line) and tissue (dashed line) compartments during selective head cooling (SHC - solid line) and whole body cooling (WBC - dashed line). During the last 20 minutes of cooling hypoxia is produced, and $PaO_2$ or $pa_o$ is reduced 82% at a rate of 5.35 mmHg/min.

D.5 Summary and Important Remarks

We studied the effect of temperature on the cerebral oxygen transport using a compartmental model that introduces the temperature dependence of the blood flow, the tissue metabolic rate and the oxygen dissociation curve. Our calculations show that mild hypothermia ($35^\circ C$) does not affect the compartmental oxygen content significantly, and that in the presence of hypoxia, temperature can be used to control the oxygen distribution in the different tissue compartments.

For the transient calculations presented here, regarding oxygen distribution during cooling and cooling with hypoxia, the need for accurate knowledge of the blood flow, metabolic activity and tissue temperature is observed. In the results of this section, such variations were taken from the literature, but better models of oxygen transport that introduce intracranial dynamics, gas transport and blood flow regulatory mechanisms are required.
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[70] M. Shadid, L. Hiltermann, L. Monteiro, J. Fontijn, and F. Van Bel. Near infrared spectroscopy-measured changes in cerebral blood volume and cytochrome $aa_3$ in 3 newborn lambs exposed to hypoxia and hypercapnia, and ischemia: a comparison


