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A thermoregulation model for hypothermic treatment of neonates

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ABSTRACT

This paper presents a thermoregulation finite element model (FEM) to simulate hypothermia procedures for the treatment of encephalopathy hypoxic-ischemia (EHI) in neonates, a dangerous ischemic condition that can cause neurological damages and even death. Therapeutic hypothermia is the only recommended technique to reduce sequels caused by EHI in neonates; intervention with moderate cooling for neural rescue in newborns with hypoxic-ischemic brain injury is the culmination of a series of clinical research studies spanning decades. However, the direct monitoring of brain cooling is difficult and can lead to additional tissue damage. Therefore, the measurement of efficiency during clinical trials of hypothermia treatment is still challenging. The use of computational methods can aid clinicians to observe the continuous temperature of tissues and organs during cooling procedures without the need for invasive techniques, and can thus be a valuable tool to assist clinical trials simulating different cooling options that can be used for treatment. The use of low cost methods such as cooling blankets can open the possibility of using brain cooling techniques in hospitals and clinics that cannot currently afford the available expensive equipment and techniques. In this work, we developed a FEM package using isoparametric linear three-dimensional elements which is applied to the solution of the continuum bioheat Pennes equation. Blood temperature changes were considered using a blood pool approach. The results of the FEM model were compared to those obtained through the implementation of a user-defined function (UDF) in the commercial finite volume software FLUENT and validated with experimental tests. Numerical analyses were performed using a three-dimensional mesh based on a complex geometry obtained from MRI scan medical images.

1. Introduction

Although the use of hypothermia as a therapeutic treatment refers to the Ancient Greece [1], only in the last century the effects of hypothermia on metabolism were better comprehended, allowing its use in the global cooling of the human body. In the last decades, the positive effects of mild hypothermia after cardiac arrest and brain trauma were observed, and only very recently these effects were studied for applications post-trauma. It has been shown that therapeutic hypothermia can minimize sequels caused by hypoxic-ischemic conditions resulting of insufficient perfusion in tissues. Under this condition, the brain is the most vulnerable tissue [1], and the first few hours after the ischemia are the critical time when secondary factors such as hypotension, hypoxia, hyperglycaemia and hyperthermia may occur and cause brain cell damage [2].

In neonates, hypothermia is the only known treatment for encephalopathy hypoxic-ischemic (EHI), a dangerous ischemic condition that can cause neurological damages and even death. EHI is usually a consequence of complications during birth such as suffocation by umbilical cord, ingestion of amniotic fluid and placenta displacement. After a consistent record of neuroprotection in animal research, induced hypothermia was investigated in several clinical trials with neonates suffering perinatal asphyxia [3].

In 2006, Edwards and Azzopardi [4] discussed extensive experimental data resulting from clinical trials for the CoolCap project [5], from the National Institute of Child Health and Human Development (NICHD) [6] and from Eicher et al. [3], and concluded that:"either selective head cooling or total body cooling reduces the combined chance of death or disability after birth asphyxia. However, as there are still unanswered questions about these

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treatments, many may still feel that further data are needed before healthcare policy can be changed to make cooling the standard of care for all babies with suspected birth asphyxia."

A database review between 1993 and 2008 [7] shows that many authors agreed that brain cooling is a promising therapeutic treatment in reducing brain damage in neonates. Eight randomized controlled trials [8] comprising 638 infants with moderate/severe encephalopathy showed a statistically significant reduction in mortality and neurodevelopmental disability in neonates after treatment.

Extensive experimental and clinical research carried out into prolonged moderate hypothermia for perinatal asphyxial encephalopathy was recently reported by Azzopardi et al. [9]. They also report data from the UK TOBY Cooling Register, which was set up immediately following the conclusion of enrolment to the TOBY (Total Body Hypothermia) trial, a multicentre randomized controlled trial of whole body hypothermia for the treatment of perinatal asphyxial encephalopathy, predominantly carried out in the UK. The TOBY Cooling Register already contains data available from 1331 reported cases.

Gluckman et al. [5] stated that a mild hypothermia treatment in neonates, at least six hours after detection of the hypoxic condition, is associated with positive neurological and physiological outcomes. Furthermore, the duration and intensity of cooling can determine the effects of the treatment in reducing damages [10]. The treatment consists in a reduction of the core temperature to 33–34 °C for 48 to 72 h and a rewarming phase at a rate of approximately 0.5 °C per hour.

Hypothermic treatment in neonates can be performed by different methods. The most widely used are selective brain cooling, which consists of a cooling helmet/cap or a pack of ice placed in the head to reduce temperature, as used in the CoolCap trials, and whole body cooling, that uses a cooling blanket to decrease the core temperature of the body, as used in the TOBY trial. Although clinical trials have shown that the hypothermic treatment reduces the sequels of perinatal asphyxia, the efficacy of the different cooling methods is hard to measure through clinical trials. Gluckman et al. [5] suggest that the first method can allow effective brain cooling to be achieved with less systemic hypothermia, reducing the adverse systemic effects of the cooling. On the other hand, clinical trials suggest that whole body cooling results in better outcome in severe EHI cases, in which selective brain cooling would not be protective [11].

Proper evaluation of the cooling procedures requires that the deep brain temperatures, where cell loss leads to the most severe long term neurological impairments, are to be measured [12]. Not only is the brain temperature difficult to measure but also, in the case of neonates, their immunological system is more fragile and the body is much more susceptible to temperature changes than adults. As their brain is still under development, the vulnerabilities and healing potential are different to that of an adult [2]. Although ischemia damages in neonates are much similar to those observed in adults, factors such as the duration of the treatment and the goal temperature may vary [10].

With the advances in the development of computational methods, the use of numerical modelling to simulate diseases and biological conditions in the human body has become an important tool to aid clinicians and researchers to understand the processes. Advances in computer modelling allow a detailed analysis of all information collected from the patient, the study of the influence of various parameters, facilitate the interpretation of the diagnosis, and enable the construction of models of a specific pathological condition and their use as a prognostic tool during treatment.

Heat transfer in the human body can be affected by several mechanisms such as environmental conditions, thermophysical properties of tissues and fluids, vascular geometry, physiological changes and pathologies [13]. Bioheat models describe the heat flux in the human body and have an important role in understanding heat transfer in human tissues. These models are usually analyzed on a macro-scale considering a continuum media composed by a mix of blood and tissues, as is the case of the Pennes model used in this work [14]. The Pennes model is one of the most popular bioheat models and assumes that heat transfer in the tissues occurs only at the capillary vessels [15]. It describes the bioheat transfer in a simple way and it was shown to be very efficient for different bioheat applications [16].

The main goal of the hypothermia treatment is to reduce the temperature in the brain. Studies simulating hypothermia in the human head purely based on bioheat models showed that, because of the influence of arterial temperature in the tissue temperature, the temperature inside the brain is not affected by external cooling [17], unless an invasive procedure such as intracarotide saline infusion is applied [18,19]. In Zhu and Diao [20] and Ley and Bayazitoglu [21], simulations of hypothermia procedures considering only the head were not effective in reducing the deep brain temperature. As the arterial temperature is responsible for regulating local tissue temperature, protecting the tissues against external cooling, the model employed to simulate hypothermia in the body must be able to take into account arterial temperature changes [22,23].

For this reason, in this paper, we adopted a model that considers thermoregulation responses as the body tries to recover the heat loss and re-establish the homoeothermic balance, reducing the efficiency of the treatment [24]. In the last decades, several models were developed to try to reproduce the thermoregulation system, from simple two-node models to more complex multi-segment models [25,26]. In Schwarz et al. [27], an 128 segment hemodynamic model developed by Avolio [28] is used as an input for a thermoregulation model based on Fiala [29] for hypothermia simulations during open heart surgery. Other examples of applications have been found in different fields, such as the automotive industry, environmental comfort and biomedical engineering [30].

The model presented in this paper was implemented in a finite element software developed at the Structures and Materials Laboratory at the Federal University of Rio de Janeiro. The idea of segments and a central blood pool is adapted from Fiala [29], but implemented here as part of a three-dimensional model which assumes that all segments are connected and exchange heat with neighbouring segments. The simulation results were compared to those presented in Laszczyk and Nowak [31], and were also validated with some available experimental results.

2. Methodology

2.1. Bioheat transfer

The transport of blood in the tissue is a difficult process to be modeled at the microscopic level due to the large amount of vessels present in the tissues. In this paper, we considered a continuum macro-scale model based on blood perfusion developed by Pennes [13]. The model considers blood and tissue as a continuous homogeneous medium. The Pennes' equation is given by

$$\rho_t c_t \frac{\partial T_t}{\partial t} = \nabla \cdot (k_t \Delta T_t) + \rho_b c_b \omega_b (T_a - T_t) + \dot{q}_m \tag{1}$$

and represents the bioheat flux in a domain Ω . In the above equation, T is the temperature and the subscripts t, b, a and m represent tissue, blood, arterial blood and metabolism, respectively. The material properties defined in the equation are: k (thermal conductivity), c (specific heat), ρ (density) and ω (blood perfusion rate). The metabolic heat generation rate is represented by $\dot{q}_m$. The perfusion term and the metabolic heat generation rate are