International Journal of Heat and Mass Transfer 51 (2008) 5662–5670

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

journal homepage: www.elsevier.com/locate/ijhmt

Targeted brain hypothermia induced by an interstitial cooling device in the rat neck: Experimental study and model validation

Yunjian Wang [a], Liang Zhu [a,*], Axel J. Rosengart [b]

[a] Department of Mechanical Engineering, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, United States
[b] Neuroscience Critical Care, New York Presbyterian Hospital, New York, NY, United States

ARTICLE INFO

Article history:
Received 21 November 2007
Received in revised form 4 April 2008
Available online 12 June 2008

Keywords:
Brain hypothermia
Ischemic brain injury
Interstitial cooling
Rat
Surgery

ABSTRACT

Targeted brain hypothermia has the potential to prevent cerebral ischemia injury during open heart and neck surgeries or after traumatic head injury. In this study, *in vivo* experiments were performed to test the performance of a newly developed cooling device in an inexpensive animal model. Rat brain hypothermia was induced by inserting an interstitial cooling device in the rat neck muscle and placing the device on the common carotid artery to cool the arterial blood supplied to the brain. Coolant was circulating inside the cooling device to achieve either mild or moderate temperature reductions at the surface of the device. Temperatures were measured inside the rat brain tissue, as well as on the head skin surface. For the mild cooling (cooling device surface temperature was 18.7 ± 4.5 °C), the temperature reductions were 2.2 ± 0.6 °C, 2.1 ± 0.6 °C, 1.9 ± 0.6 °C and 1.6 ± 0.9 °C at sites of brain-5 mm, brain-2 mm, skull, and scalp, respectively. After the surface temperature was further decreased to 12.8 ± 2.8 °C (moderate cooling), the temperature reduction in the head increased more than 85% to 3.7 ± 3.2 °C, 3.7 ± 3.0 °C, 3.3 ± 2.5 °C and 2.5 ± 1.0 °C, respectively. The experimental data were also used to validate a previously developed theoretical model for humans. Experimentally measured geometrical and physiological parameters of the rat neck and brain were substituted into the scaled-down theoretical model to simulate the temperature distribution in the rat neck and brain. The theoretically predicted brain temperatures showed a good agreement with the experiment data. We believe that this study is the first step in developing a reliable cooling device to achieve fast cooling and to control rewarming in future clinical studies and to benefit a large patient population.

1. Introduction

Neuroprotection, that is, reducing the impact of brain injury either prior to or after the occurrence of a damaging insult has the potential to greatly improve the mortality and morbidity of patients suffering from a wide variety of brain injuries. Currently, the most reliable and clinically useful neuroprotectant is cooling of the brain; for example, initiated prior to high-risk, complex cardiothoracic surgery which employs cardiopulmonary arrest and/or bypass, and hence, exposes the neural tissue to extended periods of cerebral perfusion standstill. The need to medically protect the brain in these settings has been addressed in several published investigations. A multicenter study by Roach et al. [1] reported that more than 6% of patients suffered neurological adverse events after coronary artery bypass surgery, a common procedure of revascularization of the blood supply of the heart after myocardial infarction. More subtle but equally important neuropsychological deficits or impairments in cognition were detected in more than 20% of bypass patients months after surgery [2]. The mechanism leading to brain ischemia during such surgeries often is a combinatory effect from global brain hypoperfusion, direct embolization of atherosclerotic material with cumulative occlusions of small brain arteries [3], and temporary large vessels, i.e., carotid artery. Often, these occlusions are necessitated by the surgery [4].

A significant body of literature demonstrates that even mild reductions in brain temperature, i.e., by 1 or 2 °C, are effective to reduce ongoing secondary damage in the acutely injured brain. The palliative effects directly translate into clinical benefits, mainly reductions in death and disability after brain injury. Brain hypothermia reduces tissue oxygen demands [5] and ameliorates numerous deleterious cellular biochemical mechanisms, including calcium shift, excitotoxicity, lipid peroxidation and other free radical reactions, DNA damage, and inflammation [6]. In particular, hypothermia initiated prior to or immediately after the onset of the damaging event provides potent, dose-(temperature-)related and long-lasting neuroprotection as evidenced in many experimental studies [7]. Conversely, an elevated brain temperature of

* Corresponding author. Tel.: +1 410 455 3332; fax: +1 410 455 1052.
E-mail address: zliang@umbc.edu (L. Zhu).

0017-9310/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijheatmasstransfer.2008.04.042

Nomenclature

c	Specific heat (J kg^{-1} K^{-1})
d	Distance defined in Fig. 3 (m)
e	Distance defined in Fig. 3 (m)
k	Thermal conductivity (W m^{-1} K^{-1})
h	Heat transfer coefficient (W m^{-2} K^{-1})
L	Length of the neck cylinder (m)
M	Mass (kg)
q_{loss}	Total heat loss from the arterial blood to the device per unit time (W)
q_m	Local metabolic heat generation rate (W m^{-3})
Q	Volumetric flow rate (m^3 s^{-1})
r	Radial distance from the center of the artery in cylindrical coordinates (m)
R	Radial distance from the center of the neck cylinder in cylindrical coordinates (m)
t	Time (s)
T	Temperature (°C or K)
z	Axial distance in cylindrical coordinates (m)

Greek symbols

ρ	Density (kg/m^3)
θ	Polar angle in cylindrical coordinates
ω	Local volumetric blood perfusion rate per unit volume of tissue (s^{-1})

Subscripts

a	Artery
b	Blood
bt	Brain
n	Neck
t	Tissue

only 1–2 °C strikingly worsens neuronal injury in experimental settings and has a clinically proven, negative impact on patient outcome [8].

There are two conceptual approaches to reduce brain temperature but unfortunately, only one, systemic cooling, has achieved clinical utility. Systemic cooling induces brain hypothermia by reducing the temperature of the whole body, commonly via venous blood cooling. It is an effective approach in brain injury as approximately 20% of the cardiac output (and hence, cooled blood) is delivered to the brain and modern clinical care can utilize intravascular cooling catheters to achieve powerful, rapid, and constant hypothermia induction. However, adverse events from whole body cooling predominate and curtail its clinical usefulness in a cooling depth- and time-dependent manner leading to a reversal of the benefit-risk ratio [6,9]. The second approach to brain cooling is targeted hypothermia in which the brain is selectively cooled while the rest of the body is kept euthermic. The opportunity to cool the brain selectively, thereby avoiding the main adverse events of systemic cooling such as infections and sepsis, blood clotting abnormalities, and heart and lung failure, is of great clinical and biomedical engineering interest. Employing a historically well-known method of external head cooling with ice packs or cooling wraps has led to clinical use of cooling helmets in brain-injured neonates. Recent theoretical [10,11], animal [12–14], and clinical [15] studies have demonstrated that external head cooling will not penetrate beyond the brain gray (upper surface) matter. Some of the more invasive targeted brain cooling approaches under investigation with unknown clinical usefulness include nasopharyngeal cooling, direct catheter cooling [16], and intra-carotid flushing with coolant.

An alternative approach to achieve fast and uniform temperature reduction throughout most of the brain tissue is to reduce the temperature of the carotid arteries in the neck as these vessels are responsible for about 80% of the total brain perfusion. However, a previous theoretical investigation by the author [17] delineated the ineffectiveness to reduce brain temperature via applying surface neck cooling of the carotid arteries. In contrast, if an appropriately designed cooling device is inserted safely under the skin and in physical contact with the common carotid artery (CCA), more effective brain cooling could possibly be achieved by reducing the thermal resistance between the cooling device and the artery. A previous simulation of the human neck and head using this cooling approach [18] demonstrated the theoretical feasibility of inducing at least a 3 °C temperature drop along each CCA. However, the theoretical model needs validation before the cooling device can be used in clinical studies.

Animal experiments are usually performed to test any cooling device and to measure the temperature reduction in the brain tissue. An approach to the development of a model of this cooling methodology for humans is to begin with small animal studies. A comparison of the experimentally measured data on small animals with the theoretical model for animals can be used to validate the theoretical model for the animal. In most of the animal studies of a medical device, model validation is necessary to assess the accuracy of the theoretical model in handling complicated and realistic structures such as the brain or neck. Once the theoretical model is validated in small rodents, experimental studies can be conducted on large animals. This approach provides confidence that the cooling capacity applied to human anatomy is accurate and reliable before the device can be used in future clinical studies.

Based on the encouraging results obtained from our previous theoretical work [18], we now utilized *in vivo* rodent experiments to report on brain hypothermia induction and distribution during direct CCA cooling and compare the obtained results to our previously obtained simulations. A compact neck cooling device, made from flexible two-dimensional cooling sheets, was designed and brought in direct physical contact with both common carotid arteries of anesthetized rats. The temperature distribution in the brain tissue was measured and the effects of variations in coolant temperature were evaluated. In our analyses, we included the detailed vascular geometry and blood flow rates of the test animals and, based on the obtained data, we extended and validated the previously reported theoretical model to accurately simulate the temperature fields in the neck and brain of the animal.

2. Materials and methods

In vivo experiments were performed to measure the transient brain temperature distributions and to determine the temperature reductions at various brain tissue locations after inserting a specifically designed cooling device with close proximity to the CCA into the neck of anesthetized rats. The feasibility of inducing hypothermia via direct CCA cooling was *a priori* defined as brain hypothermia (34 °C) within 40 min of cooling.

Six Sprague-Dawley rats (456 ± 26 g, males) provided by Charles River Laboratory (Wilmington, MA) were used. At the beginning of the experiment, each rat was anesthetized and maintained in sedation with intraperitoneal injections (i.p.) of sodium