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Brain cooling maintenance with cooling cap following induction with intracarotid cold saline infusion: A quantitative model

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ABSTRACT

Intracarotid cold saline infusion (ICSI) is potentially much faster than whole-body cooling and more effective than cooling caps in inducing therapeutic brain cooling. One drawback of ICSI is hemodilution and volume loading. We hypothesized that cooling caps could enhance brain cooling with ICSI and minimize hemodilution and volume loading. Six-hour-long simulations were performed in a 3D mathematical brain model. The Pennes bioheat equation was used to propagate brain temperature. Convective heat transfer through jugular venous return and the circle of Willis was simulated. Hemodilution and volume loading were modeled using a two-compartment saline infusion model. A feedback method of local brain temperature control was developed where ICSI flow rate was varied based on the rate of temperature change and the deviation of temperature to a target (32 °C) within a voxel in the treated region of brain. The simulations confirmed the inability of cooling caps alone to induce hypothermia. In the ICSI and the combination models (ICSI and cap), the control algorithm guided ICSI to quickly achieve and maintain the target temperature. The combination model had lower ICSI flow rates than the ICSI model resulting in a 55% reduction of infusion volume over a 6 h period and higher hematocrit values compared to the ICSI model. Moreover, in the combination model, the ICSI flow rate decreased to zero after 4 h, and hypothermia was subsequently maintained solely by the cooling cap. This is the first study supporting a role of cooling caps in therapeutic hypothermia in adults.

1. Introduction

Hypothermia has been shown to reduce infarct volume and improve neurologic outcomes in animal models of focal cerebral ischemia (Chen et al., 1992). It has also improved survival and functional outcomes in randomized clinical trials involving patients with global cerebral ischemia after cardiac arrest (Bernard et al., 2002; The Hypothermia After Cardiac Arrest (HACA) Study Group, 2002). In most clinical studies, hypothermia is induced by surface cooling. While this is the simplest and most cost-effective method of inducing hypothermia (Feigin et al., 2003), it has a major limitation. Surface cooling requires 3–7 h to reach the target brain temperature of 32–34 °C (Kammersgaard et al., 2000; Schwab et al., 2001). Although intravenous whole-body cooling may be able to accelerate the induction of hypothermia, this method is still reported require 2–4.5 h to achieve target temperature (Georgiadis et al., 2001) Further, in clinical trials of this method not all patients were cooled to target temperature (De Georgia et al., 2004; Lyden et al., 2005). Hundreds of animal studies on hypothermia induction, as well as randomized trials on intravenous thrombolysis have demonstrated the efficacy of treatment only within 3 h after the onset of symptoms (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Konstas et al., 2006). Hence, whole-body cooling induction will miss the 3-h therapeutic window in the majority of stroke patients.

Selective brain cooling (SBC) may be able to induce hypothermia faster than whole-body cooling methods. Different methods for SBC exist (Harris and Andrews, 2005). The non-invasive methods most commonly used are cooling caps and helmets. However, theoretical analyses (Diao et al., 2003; Nelson and

Abbreviations: A1, proximal segment of anterior cerebral artery; A2, distal segment of anterior cerebral artery; ACA, anterior cerebral artery; BA, basilar artery; CoW, circle of willis; ICA, internal carotid artery; *HCT*, hematocrit; *IAT*, ipsilateral anterior territory; ICSI, intracarotid cold saline infusion; *MAP*, mean arterial pressure; MCA, middle cerebral artery; P1, proximal segment of posterior cerebral artery; P2, distal segment of posterior cerebral artery; PCA, posterior cerebral artery; SBC, selective brain cooling.

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Nomenclature

∇	gradient operator
$\nabla\cdot$	divergence operator
∂	partial differentiation operator
$\iiint$	volume integration
ρ	density ($kg\,m^{-3}$)
κ	control constant ($m^3\,s^{-1}\,{}^{\circ}C^{-1}$)
π	≈ 3.1416
τ	time constant (s)
η	viscosity ($kg\,m^{-1}\,s^{-1}$)
Δ	change from baseline
ω	cerebral blood perfusion ($ml\,min^{-1}\,hg^{-1}$)
c	heat capacity ($J\,kg^{-1}\,K^{-1}$)
d	differentiation operator, vessel diameter (m)
e	≈ 2.7183
h	convective heat transfer coefficient
H	catheter heat transfer coefficient ($m^3\,s^{-1}$), heat (J)
k	heat conductivity ($W\,m^{-1}\,K^{-1}$)
k	flow rates, and flow rate parameters for hemodilution model ($m^3\,s^{-1}$)
m	mass (kg)
q	metabolism, heat production ($W\,m^{-3}$)
r	radius
$\vec{r}$	three-dimensional spatial location
t	time (s)
F	flow ($m^3\,s^{-1}$)
G	vascular conductivity ($kg^{-1}\,m^4\,s$)
L	vessel length (m)
P	pressure ($kg\,m^{-1}\,s^{-2}$)
T	temperature (°C)
V	volume (m^3)

Subscripts

0	baseline
1	arbitrary adjacent vessel junctions (P), intravascular fluid space (v, V)
2	arbitrary adjacent vessel junctions (P), peripheral fluid space (v, V)
b	basal fluid loss
cACA	contralateral anterior cerebral artery
cMCA	contralateral middle cerebral artery
cPCA	contralateral posterior cerebral artery
i	infusion flow (k)
ICA	internal carotid artery
iACA	ipsilateral anterior cerebral artery
iMCA	ipsilateral middle cerebral artery
iPCA	ipsilateral posterior cerebral artery
B	combined basilar and verterbral (G)
IV	Intravascular
*IV*0	baseline intravascular
r	urine flow rate parameter
RBC	red blood cell
t	transfer flow parameter between intravascular and peripheral volumes

Nunneley, 1998; Sukstanskii and Yablonskiy, 2007) and empirical measurements (Corbett and Laptook, 1998; Mellergard, 1992; Wang et al., 2004; Zhu et al., 2006) suggest that they are only effective in reducing the temperature in superficial cerebral regions and not deep brain structures. These studies demonstrated that head surface cooling is ill conceived because brain is highly perfused by warm blood, which severely limits the conductive penetration of surface cooling. Another SBC method is intracarotid cold saline infusion (ICSI) where cold saline is infused into the internal carotid artery (ICA) via transfemoral catheterization. This method is potentially much faster than whole-body cooling and more effective than surface SBC. Two recent theoretical studies addressed the clinical feasibility of ICSI for inducing hypothermia (Konstas et al., 2007; Neimark et al., 2007). A three-dimensional mathematical model was developed to examine the transient and steady-state temperature distribution in the human brain during ICSI. A healthy brain and a brain with ischemic stroke were modeled. The complete Circle of Willis (CoW) and two common CoW variants were incorporated in the model, taking into account the effect of cooled jugular venous blood returning to the body core. In the simulations, an infusion rate of $30\,ml\,min^{-1}$ was sufficient to induce moderate hypothermia (defined as 32–34 °C) within 5–10 min in the ipsilateral hemisphere. These theoretical analyses suggested that this efficiency of hypothermia induction was also efficient in brains with stroke and/or common CoW variants.

The drawback of ICSI is the length of time hypothermia can be maintained due to safety concerns. One such concern is the increasing local and systemic hemodilution that results from a constant infusion of $1800\,ml\,h^{-1}$ of isotonic saline. One effect of brain cooling is an exponential decrease of cerebral perfusion due to coupling of metabolism, and perfusion in the brain (Ehrlich et al., 2002). It is conceivable that if head surface cooling were to be attempted in addition to ICSI, cerebral perfusion in the brain would be further decreased enough in the head so that less saline would need to be infused to induce and maintain SBC.

In the present study, a method of controlling brain temperature by modulating cold saline flow during SBC is presented. If SBC is to be implemented clinically, it will be necessary to utilize control methods that maintain brain temperature at a target temperature over the length of the therapy period. This control method also allows comparison between cooling protocols involving ICSI alone, and combination ICSI and cooling cap by comparing the amount of saline flow necessary to maintain target temperature.

Three different methods of SBC are simulated theoretically: Cooling cap alone, ICSI alone and a combination of ICSI and cooling cap. In methods involving ICSI, the control algorithm was employed to target and maintain hypothermia at 32 °C. This temperature was utilized because it was the lowest target temperature employed in human hypothermia stroke trials (Krieger et al., 2001) and as such would provide the largest challenge in terms of maintaining safe intravascular volumes and hematocrits. In the simulation, hypothermia was continued for 6 h, the minimum time-length of hypothermia maintenance in pilot human studies (Kammersgaard et al., 2000). This study addresses three questions concerning SBC: First, whether the control algorithm can guide saline infusion to quickly achieve target temperature and maintain it in a stable fashion. Second, whether utilization of a cooling cap can enhance brain cooling with ICSI. Third, if the cooling cap application can minimize the ICSI flow rate with subsequent reduction in the degree of hemodilution resulting from ICSI during the 6-h hypothermia maintenance.

2. Methods

2.1. Brain model

A 3D hemispheric head model was developed in spherical coordinates. This model consists of four tissue layers: white