Proceedings of the 29th Annual International
Conference of the IEEE EMBS
Cité Internationale, Lyon, France
August 23-26, 2007.

Local Control of Temperature in a Theoretical Human Model of Selective Brain Cooling

Matthew A. Neimark, Angelos-Aristeidis Konstas, Jae H. Choi, Andrew F. Laine, and John Pile-Spellman

Abstract— **A method of feedback control of local brain temperature during therapeutic intracarotid cold saline infusion is presented and tested on a theoretical cerebral heat transfer model based on the Pennes bioheat equation. In this temperature control method, the infusion rate of cold saline is varied based on the rate of temperature change, and the deviation of temperature to a target, within a voxel in the treated region of brain. This control method is tested in cases where the head is exposed to ambient room temperature, and where the head is packed in ice. In both the ice and non-ice cases, target temperature (33 ºC) is achieved in the voxel according to the desired time constant (2 minutes). Two hours of treatment decreased the required inflow of ice-cold saline from 30 ml/min to 21 and 7 ml/min in the non-ice and ice cases, respectively. Intracarotid hematocrit had higher values in the non-ice case.**

I. Introduction

Therapy for ischemic stroke remains a major challenge in medicine. Hypothermia is an encouraging treatment. It has already proven beneficial in treating global ischemia resulting from cardiac arrest [1]. Further, it has demonstrated positive results in treating focal ischemia resulting from stroke in animal studies [2] and small clinical series [3].

Current methods of inducing hypothermia include surface cooling methods [4] and inferior vena cava closed-loop catheters [5]. Surface cooling can exceed 6 hours to achieve target temperature and even inferior vena cava catheters, which have been developed to cool quickly, require, on average, 1-3 hours to achieve therapeutic temperatures. These cooling times can cause patients to miss the time limit by which any therapy can be effective. The other problem with systemic cooling is side effects such as arrhythmia, infections, and coagulopathies [3].

Selective brain cooling techniques have been attempted in the form of cooling caps and ice packs. However, these techniques have largely failed [6, 7]. Recent theoretical developments have also demonstrated that surface selective brain cooling is ill conceived because brain is highly perfused by warm blood, which severely limits the conductive penetration of surface cooling [8].

Recently, a method of brain cooling has been proposed which utilizes an intracarotid cold saline infusion (ICSI) [9]. It was theoretically determined that an infusion rate of 30 ml/min could be utilized to achieve therapeutic temperature levels of 32-33 ºC. The drawback of this method is the length of time hypothermia could 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/hr 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 [10]. There is thus a possibility that if brain cooling were to be attempted with a combination of ICSI and head surface cooling, cerebral perfusion in the brain would be decreased enough in the head so that penetration depths of the surface cooling would be increased, and surface cooling could effectively contribute to the entire cooling effect in the brain.

One way to test the effectiveness of surface cooling would be to clamp temperature at a certain level, and vary flow rate to maintain this temperature. If surface cooling were effective, a lower saline flow rate would be necessary to maintain target temperature than if there was no surface cooling.

In any case, if ICSI therapy is to be implemented clinically, it will be necessary to utilize control methods to maintain brain temperature at a target temperature over the length of the therapy period.

In the present study, a method of controlling brain temperature during ICSI is presented. It is then theoretically tested on the brain cooling method both in cases where ice packs applied to the head and in cases where the head is exposed in ambient room temperature. This study addresses 1) whether the control algorithm can guide saline infusion to quickly achieve target temperature and maintain it in a stable fashion, 2) whether surface cooling is more effective in the presence of endovascular cooling, 3) the degree to which hematocrit levels can be maintained within safe levels given longer infusion times than previously attempted.

II. Methods

A. Brain Model

A 3D hemispheric head model was developed in spherical coordinates. This model consists of four tissue layers: white matter, gray matter, skin, and bone (Fig. 1). For every

Manuscript received April 12, 2007.

M. A. Neimark and A. F. Laine are with the department of Biomedical Engineering, Columbia University, New York, NY 10027 USA (phone: 212-854-5996; fax: 212-854-5995; e-mail: al418@ columbia.edu).

A. A. Konstas and J. Pile-Spellman are with the Department of Radiology, Columbia University, New York, NY 10032 USA (e-mail: jp59@ columbia.edu).

coordinate within the head model, there is an associated variable temperature T, metabolism q, and perfusion ω. Constant biothermal parameters corresponding to each coordinate are density ρ, specific heat c, and thermal conductivity k.

In the brain tissues, metabolism and perfusion are related to temperature by $q = q_0 \cdot 3.0^{0.084(T-37)}$ (1) [9] and $\omega = \omega_0 \cdot 3.0^{0.084(T-37)}\left(1 - 2.2\Delta_{HCT}\right)$ (2) due to metabolic coupling. In the skull and scalp these two parameters are constant. Below 28 ºC, flow is no longer coupled to temperature [11], so the equation becomes $\omega = \omega_0 \cdot 3.0^{0.084(-9)}\left(1 - 2.2\Delta_{HCT}\right)$ (3).

Temperature in the model evolves according to the Pennes bioheat equation:

$$\frac{\partial T(\vec{x},t)}{\partial t} = \frac{\nabla\cdot\left[k(\vec{x})\nabla T(\vec{x},t)\right]}{\rho(\vec{x})c(\vec{x})} + \frac{\rho_{blood}c_{blood}}{\rho(\vec{x})c(\vec{x})}\omega(\vec{x},t)\left[T_{artery}(\vec{x},t) - T(\vec{x},t)\right] + \frac{q(\vec{x},t)}{\rho(\vec{x})c(\vec{x})} \quad (4)$$

[12] where $\vec{x}$ is the spatial coordinate and T_{artery} is the temperature of the blood that perfuses the tissue at that point.

At the surface of the head model, at the interface between scalp and air, heat transfer is described by the following boundary condition: $k\frac{\partial T}{\partial r} = -h_{air}\left(T - T_{air}\right)$ (5) where h_{air} is the heat transfer coefficient between the scalp and air. If the head is packed in ice, the surface temperature is instead set to 0 ºC and the boundary condition becomes $T = 0$.

Cooled venous blood returns from the head and cools the body core according to:

$$\frac{dT_{core}}{dt} = \frac{\rho_{blood}c_{blood}\left(T_{venous} - T_{core}\right)\iiint_{brain\,model}\omega(\vec{r})d\vec{r}}{m_{body}c_{body}} \quad (6)$$

where T_{venous} is described by: $T_{venous} = \iiint_{Brain\,Model}\omega(\vec{r})T(\vec{r})d\vec{r} \Big/ \iiint_{Brain\,Model}\omega(\vec{r})d\vec{r}$ (7). Further details of the brain model, including boundary conditions for solving (4) have been previously described [9].

B. Saline Infusion

Saline is infused through the ipsilateral internal carotid artery (ICA). There, it mixes with the inflowing blood, forming a perfusate with temperature:

$$T_{ICA} = \frac{\rho_{blood}c_{blood}F_{ICA}\cdot T_{core} + \rho_{saline}c_{saline}F_{saline}\cdot T_{saline}}{\rho_{blood}c_{blood}F_{ICA} + \rho_{saline}c_{saline}F_{saline}} \quad (8)$$

and hematocrit

$$HCT_{ICA} = \frac{F_{ICA}\cdot HCT_{systemic}}{F_{ICA} + F_{saline}} \quad (9)$$

where F_{ICA} is blood flow rate in the ipsilateral ICA and F_{saline} is the saline flow rate.

Inflowing blood through the other source vessels (contralateral ICA and basilar artery) has blood with systemic hematocrit and core body temperature. Perfusate from the ipsilateral ICA is then redistributed through the circle of Willis (Fig. 1) where it mixes with this other blood according to a linear model based on Kirchoff's circuit laws. This model is described more fully in another study [13].

Systemic hematocrit is decreased by saline infusion according to $\Delta_{HCT} = \frac{0.42\cdot V_{RBC}\Delta V_{IV}}{V_{IV0}\left(V_{IV0} + 0.42\cdot\Delta V_{IV}\right)}$ (10) [9]

where V_{RBC} is the red blood cell volume, V_{IV0} is the initial intravascular volume, ΔV_{IV} is the volume of added saline.

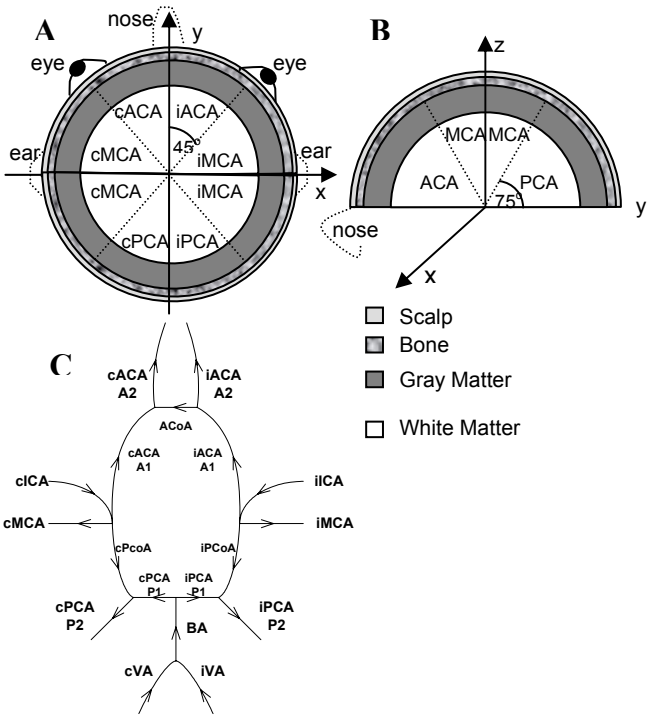

Fig. 1. Brain perfusion model. **A** Axial slice at base of brain model demonstrating tissue layers and boundaries of perfusion territories corresponding to feeding arteries from the circle of Willis. **B** Paramedian slice of brain model. **C** Diagram of Circle of Willis showing normative flow patterns(top – axial view and bottom –paramedian view) showing four tissue layers and demarcation of perfusion territories. Source vessels include the internal carotid arteries (ICA) and vertebral arteries (VA) which join to form the basilar artery (BA). CoW vessels include the anterior communicating artery (AcoA), A1 branch of the anterior cerebral artery (ACA), posterior communicating artery (PCoA), and P1 branch of the posterior cerebral arteries. CoW efferent vessels, which perfuse brain tissue, include the A2 branches of the ACA and PCA, and the middle cerebral artery MCA. Prefix "i" implies ipsilateral while "c" implies contralateral.

C. Control of Saline Infusion

The control procedure involved attempting to force the temperature to follow an exponential profile. This approach was based on the fact that the temperature profiles with a constant flow infusion have an approximately exponential profile, although a true steady state is never reached [9, 13]. However, after a certain time point, temperature changes are more slowly varying. In any case the goal of this temperature control procedure is to 1) control the flow during the initial stages of infusion to achieve target temperature within a desired time period, and 2) maintain target temperature after it is achieved.

Temperature is monitored in a 4.7 ml voxel located in the middle of the ipsilateral anterior territory (45º from the base of the brain in the azimuth direction and 45º in the anterior direction from the anterior-posterior midline) and containing

approximately half white matter and half gray matter. In principle, MRI spectroscopy could be used to non-invasively measure the temperature in this voxel. In the model, T_{voxel}, was the average temperature in the volume of this voxel, and was sampled in the simulation once per second.

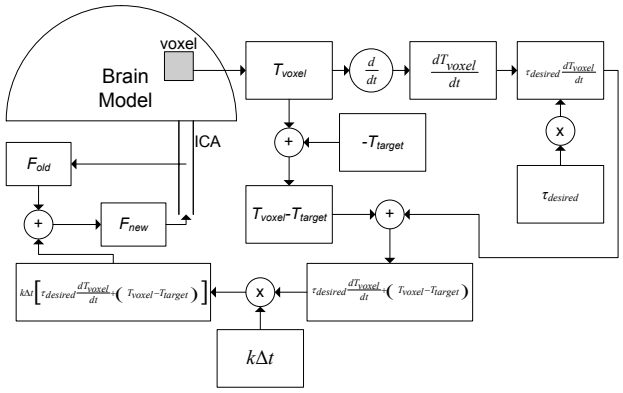

Fig. 2. Infusion flow control model. Voxel temperature is sampled. Its derivative, multiplied by the desired time constant, is compared with its deviation from the target temperature. This difference is then multiplied by kΔt and then added to the old saline flow rate F_{old} to determine the new flow rate F_{new}. ICA – internal carotid artery.

The desired temperature profile of the voxel is an exponential expressed as:

$$T_{voxel}(t) = \left(T_{voxel0} - T_{target}\right)e^{-t/\tau_{desired}} + T_{target} \quad (11)$$

where T_{voxel0} is the initial voxel temperature, T_{target} is the target temperature, and $\tau_{desired}$ is the desired time constant of cooling (i.e. the time by which 63% of cooling should have taken place).

(11) is the solution to the differential equation:

$$\frac{dT_{voxel}}{dt} - \frac{\left(T_{target} - T_{voxel}\right)}{\tau_{desired}} = 0 \quad (12)$$

. Therefore, any difference between $\frac{dT_{voxel}}{dt}$ and $\frac{\left(T_{target} - T_{voxel}\right)}{\tau_{desired}}$ implies that that the voxel cooling is not "on track" for the desired speed of cooling. Further, after T_{target} has been achieved, $\frac{dT_{voxel}}{dt}$ should be zero.

There are two parameters in ICSI which can be altered to affect brain temperature: 1) infusate inflow temperature and 2) infusate flow. Outflow saline temperature relates to these parameters according to:

$$T_{saline} = \left(T_{saline\_in} - T_{core}\right)e^{-2\pi \cdot hl / F_{saline}\rho_{saline}c_{saline}} + T_{core} \quad (13)$$

where T_{saline_in} is the saline temperature infused at the beginning of the catheter, T_{saline} is the outflow saline (as in *Eq.* 8), l is the length of the catheter, and h is the heat transfer coefficient between the catheter and body.

Of these two parameters, it is far more practical to modify infusate flow, F_{saline}, during an ICSI procedure. However, the resultant temperature T_{voxel}, would be difficult to predict *a priori*. However, it is clear from previous studies [9, 13] and theoretical considerations (i.e. *Eqs.* 4, 8, and 13) that increasing F_{saline} should decrease $\frac{dT_{voxel}}{dt}$ and vice versa. Further, although the exact relationship between ΔF_{saline} and $\frac{dT_{voxel}}{dt}$ is unknown, it must be monotonic. Therefore, F_{saline} can be modified according to:

$$\frac{dF_{saline}}{dt} = k\left[\tau_{desired}\frac{dT_{voxel}}{dt} - \left(T_{target} - T_{voxel}\right)\right] \quad (14)$$

In our simulations, $\tau_{desired}$=120 s and k=200 ml/(min·ºC). Target temperature is 33 ºC, saline inflow temperature is 0 ºC, and initial flow rate is 50 ml/min. Simulations with and without the head packed in ice (see Eq. 4). A diagram of the control model is shown in Fig. 2.

III. Results

Temperatures from the simulations are shown in Fig. 3. Voxel temperature decreased according to the desired time constant for both the case with the head packed in ice and where the head was not packed in ice (voxel temperature did not vary between these two cases). Mean ipsilateral anterior temperatures (IAT), average temperatures of the perfusion region of the ipsilateral middle and anterior cerebral arteries which has the highest perfusion from the ICA (Fig. 1) are also shown in Fig. 2. For the non-ice case mean IAT reached a steady state temperature of approximately 33.5 ºC whereas the steady state temperature for the ice case was approximately 32 ºC. The ice case reached a lower mean IAT because of lower gray matter temperatures in the periphery of gray matter where the minimum temperature fell to 21.1 ºC. The minimum gray matter temperature for the non-ice case was 32.8 ºC. The mean IAT was slightly higher because of higher temperatures at boundaries between perfusion territories. Body temperature decreased over the course of the 2 hour simulations both for the ice (~3 ºC/min) and non ice case (~1.5 ºC/min).

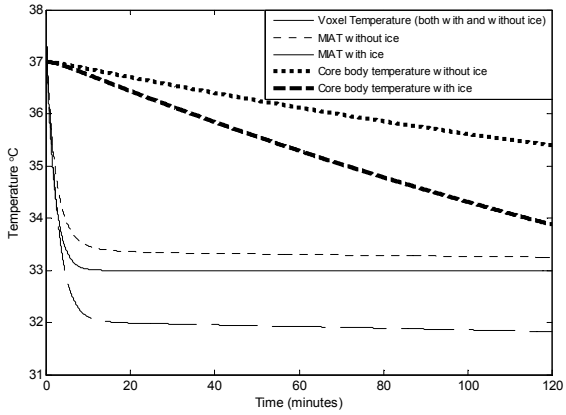

Fig. 3. Voxel, core body, and mean ipsilateral anterior temperatures in intracarotid saline infusions where infusion flow rate was controlled to maintain voxel temperature at 33 ºC for cases where head was and was not packed in ice. MIAT – mean ipsilateral anterior temperature.

Fig. 4 shows the evolution of infusion flow rates over the course of the ice and non-ice simulations. Initial flow rate was actually 50 ml/min, but for both cases this fell, within 1 minute, to approximately 30 ml/min. After rising very slightly, in order to maintain the intensive desired time

constant of the temperature drop, flow continuously decreases because of the body temperature drop. For the non-ice case, about 21 ml/min of infusion were necessary to maintain the voxel temperature at 33 ºC whereas in the ice case, only 7 ml/min were necessary.

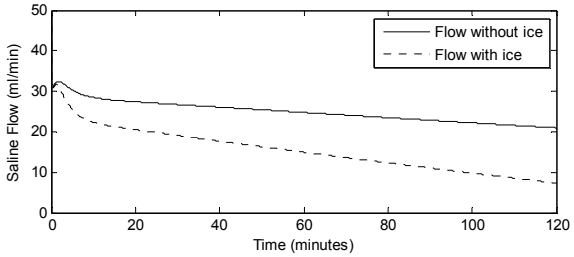

Fig. 4. Flow rates for intracarotid cold saline infusions where infusion flow rate was controlled to maintain voxel temperature at 33 ºC for cases where head was and was not packed in ice.

Fig. 5 shows local (see Eq. 9) and systemic hematocrit (from Eq. 10). These results show that even after two hours, hematocrit stays in a very safe range above 30%. For the ice case, local hematocrit remains above 34% and even begins to increase at the end as the infusion flow rate decreases substantially.

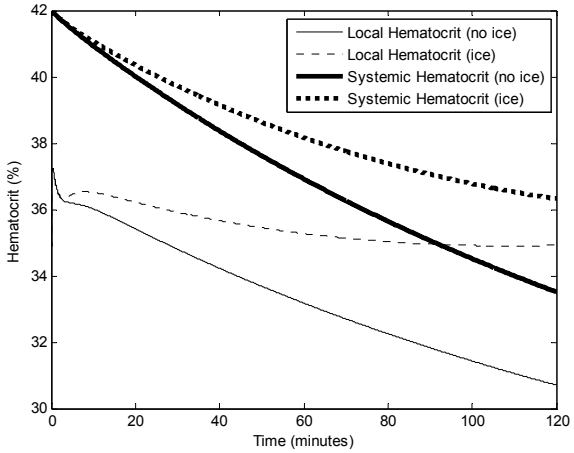

Fig. 5. Local and systemic hematocirt for intracarotid cold saline infusions where infusion flow rate was controlled to maintain voxel temperature at 33 ºC for cases where head was and was not packed in ice.

IV. Conclusions

This study demonstrates a method of controlling brain temperature in a theoretical model of brain cooling by varying the infusion rate through a feedback mechanism. This method was able to both control the cooling rate and maintain brain temperature at the target level.

This study also demonstrated that the required infusion rate to maintain temperature at the desired level decreased over the course of the treatment period due to decreased core body temperature. In the case where the head is packed in ice, much less saline infusion was necessary to maintain the brain at the desired temperature. The disadvantage of using ice was lower systemic temperatures and very low gray matter temperatures in the periphery.

In both cases hematocrit (both systemic and local) always remained above 30% over the course of a 2 hour infusion. However, the transient profiles of hematocrit suggest that over longer treatment times the local hematocrit of the non-ice case may fall to the low 20s or even below and compromise patient safety.

References

[1] M. Holzer, S. A. Bernard, S. Hachimi-Idrissi, R. O. Roine, F. Sterz, M. Mullner, and A. on behalf of the Collaborative Group on Induced Hypothermia for Neuroprotection After Cardiac, "Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis.[see comment]," *Critical Care Medicine,* vol. 33, pp. 414-8, 2005.

[2] A. A. Konstas, J. H. Choi, and J. Pile-Spellman, "Neuroprotection for ischemic stroke using hypothermia," *Neurocritical Care,* vol. 4, pp. 168-78, 2006.

[3] S. Schwab, S. Schwarz, M. Spranger, E. Keller, M. Bertram, and W. Hacke, "Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction.[see comment]," *Stroke,* vol. 29, pp. 2461-6, 1998.

[4] D. W. Krieger, M. A. De Georgia, A. Abou-Chebl, J. C. Andrefsky, C. A. Sila, I. L. Katzan, M. R. Mayberg, and A. J. Furlan, "Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke," *Stroke,* vol. 32, pp. 1847-54, 2001.

[5] M. A. De Georgia, D. W. Krieger, A. Abou-Chebl, T. G. Devlin, M. Jauss, S. M. Davis, W. J. Koroshetz, G. Rordorf, and S. Warach, "Cooling for Acute Ischemic Brain Damage (COOL AID): a feasibility trial of endovascular cooling," *Neurology,* vol. 63, pp. 312-7, 2004.

[6] R. J. Corbett and A. R. Laptook, "Failure of localized head cooling to reduce brain temperature in adult humans," *Neuroreport,* vol. 9, pp. 2721-5, 1998.

[7] P. Mellergard, "Changes in human intracerebral temperature in response to different methods of brain cooling," *Neurosurgery,* vol. 31, pp. 671-7; discussion 677, 1992.

[8] M. Zhu, J. J. Ackerman, A. L. Sukstanskii, and D. A. Yablonskiy, "How the body controls brain temperature: the temperature shielding effect of cerebral blood flow," *Journal of Applied Physiology,* vol. 101, pp. 1481-8, 2006.

[9] M. A. Neimark, A. A. Konstas, A. F. Laine, and J. Pile-Spellman, "Theoretical model of selective cooling using intracarotid cold saline infusion in the human brain," *Journal of Applied Physiology,* vol. [Epub ahead of print], December, 2006 2006.

[10] M. P. Ehrlich, J. N. McCullough, N. Zhang, D. J. Weisz, T. Juvonen, C. A. Bodian, and R. B. Griepp, "Effect of hypothermia on cerebral blood flow and metabolism in the pig," *Annals of Thoracic Surgery,* vol. 73, pp. 191-7, 2002.

[11] J. D. Michenfelder and J. H. Milde, "The relationship among canine brain temperature, metabolism, and function during hypothermia," *Anesthesiology,* vol. 75, pp. 130-6, 1991.

[12] H. H. Pennes, "Analysis of tissue and arterial blood temperature in the resting human forearm," *Journal of Applied Physiology,* vol. 1, pp. 93-122, 1948.

[13] M. A. Neimark, A. A. Konstas, J. H. Choi, A. F. Laine, and J. Pile-Spellman, "The Role of Intracarotid Cold Saline Infusion on a Theoretical Brain Model Incorporating the Circle of Willis and Cerebral Venous Return," in *29th IEEE EMBS Annual International Conference*, Lyon, 2006.