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ORIGINAL ARTICLE

Targeted brain hypothermia induced by an interstitial cooling device in human neck: theoretical analyses

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Abstract In this study, the feasibility of a newly developed interstitial cooling device inserted into the neck muscle and placed on the surface of the common carotid artery is evaluated. A combination of vascular model and continuum model is developed to simulate the temperature fields in both the neck and brain regions. Parametric studies are conducted to test the sensitivity of various factors on the temperature distribution. It has been shown that the length of the device, temperature of the device, and the tissue gap between the device and the blood vessel are the dominant factors that determine the effectiveness of this cooling approach. Under the current design parameters, the device is capable of inducing a temperature drop of 2.8°C along the common carotid artery and it results in a total of 90 W of heat carried away from the arterial blood. Although the degree of the cooling in the arterial blood is inversely proportional to the blood flow rate of the arteries, the total heat loss from the arterial blood does not vary significantly if the blood flow rate changes during the cooling. After the cold arterial blood is supplied to the brain hemisphere, temperature reduction in the brain tissue is almost uniform and up to 3.1°C temperature drop is achieved within 1 hour. In addition to the possible benefits of brain hypothermia for stroke or head injury patients, the device has the potential to control fever as well as to improve patients' outcome during open neck and head surgery.

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Introduction

Brain ischemia due to stroke or head injury remains a major cause of mortality and morbidity worldwide. Stroke is the third largest cause of death in the United States, ranking behind heart disease and cancer. It is the leading cause of serious, long-term disability in the United States. In recent years, clinical and animal studies have demonstrated neuroprotection of brain hypothermia in patients suffering cerebral ischemia and traumatic head injury. It has been shown that a reduction in brain temperature as small as 2°C reduced substantially ischemic damage (Clarke et al. 1996), and therefore, improved significantly outcome in patients with stroke, head injury or after cardiac arrest (Wass et al. 1995). Researchers have suggested that the main benefits of brain hypothermia are associated with reduction of tissue oxygen demands and slow process of deleterious cellular biochemical mechanisms, including calcium shift, release of free radicals, DNA damage, and inflammation.

The major challenge facing the clinicians to maximize the protective effect of brain hypothermia is timely delivery of this type of therapy. One approach is to cool the entire body. In this approach the heart is ultimately cooled and therefore, the temperature of the arterial blood supplying the brain is also reduced. Most of the currently used clinical studies have examined only systemic (whole body) hypothermia. The major methodological drawback of this approach is slow cooling rate (~0.5°/h) due to the large volume of the human body and arteriovenous shunt vasoconstriction (Marion et al. 1997). To induce a fast cooling

rate, a vena-venous extracorporeal blood cooling was proposed recently (Dae et al. 2003; Georgiadis et al. 2001). This method uses a cooling catheter which is inserted into the femoral vein and advanced to the inferior vena cava. Coolant is pumped to the catheter to achieve a fast cooling (1.4–7°C/h) of the venous blood with a cooling capacity of 90 W. The surgical procedure involved is invasive and vessel access time varies greatly with skill of the surgeon, so its clinical use has been limited to special hospitals (Georgiadis et al. 2001). With either technique, the major drawback of whole body cooling is that it may produce deleterious systemic effects such as metabolic, cardiovascular, pulmonary, coagulation, and immunologic complications (Marion et al. 1997). The increased risk of systemic complications when using whole body hypothermia may outweigh the neuro-protective benefits of such therapy.

Cooling the entire body or the total cardiac arterial blood to achieve a temperature reduction in brain may not be necessary, since human brain represents only 2% of body weight and it receives 20% of resting cardiac output. The long cooling time experienced by clinicians may be greatly reduced if only the head is cooled. As an alternative, in recent years, targeted brain hypothermia in which the brain is selectively cooled while the rest of the body is kept at a normal temperature has attracted a lot of attention since it is the brain tissue that needs to be cooled for ischemic or head injury patients. Currently, targeted brain cooling protocols include easily implemented approaches such as using a cooling helmet or packing the head with ice, and invasive approaches such as nasophyaryngeal cooling and intra-carotid flushing. Recent theoretical (Diao et al. 2003; Zhu and Diao 2001), animal (Allers et al. 2006; Battin et al. 2003; Diao and Zhu 2006), and clinical (Wang et al. 2004) studies have demonstrated the feasibility of cooling the brain gray matter via head surface cooling. The cooling time required is less than 1 h. However, head surface cooling provides more preferential cooling of the superficial areas of the brain than the deep regions. Large temperature gradients occur in the brain tissue and temperature variation depends strongly on the local blood perfusion rate and other factors. Temperature variation in brain tissue makes the control of the cooling extent in a targeted tissue region a difficult task. The invasive approaches in targeted brain hypothermia all aim at cooling the carotid arterial blood supplied to the brain tissue. However, nasophyaryngeal cooling may not be effective, while intra-carotid flushing is a very invasive surgical procedure and often requires considerable technical skills and specific equipment.

Cooling is a process of heat transfer from a high temperature region to a low temperature region. To achieve an effective cooling of one region, two things are critical. One is temperature difference ΔT and the other is thermal resistance R_t between the high and low temperature regions. Heat transfer rate q can then be calculated by $\Delta T/R_t$. In most of the cooling approaches, achieving a large temperature difference ΔT is not difficult since the temperature of the coolant can be as low as 0°C (ice–water mixture). To carry heat away from the high temperature region (such as the arterial blood at 37°C), it is important to decrease the thermal resistance R_t, which is usually determined by the thermal conductive tissue in between and the convection of the arterial blood. In most of the cooling protocols, the conductive resistance due to tissue is the dominant factor since heat has to travel a long distance from a high temperature region (such as heart) to a low temperature region (such as skin). A previous theoretical study by the author (Zhu 2000) has shown the in-effectiveness of reducing the temperature of the carotid arterial blood via neck surface cooling unless the blood vessel is located very close to the skin surface. Based on these considerations, in this study we develop an interstitial cooling device to reduce significantly the thermal resistance by ensuring a close physical contact between the coolant and the arterial blood and maximizing the contact surface area.

The objective of this paper is to evaluate the feasibility of inducing at least 2.0°C of temperature drop along the common carotid artery by such a cooling device. The device is designed to be inserted into the neck muscle and placed on the surface of the common carotid artery. A combination of vascular model and continuum model is developed to simulate the temperature fields in both the neck and brain regions. Parametric studies are conducted to test the sensitivity of the temperature distribution to various design parameters. Based on the simulation, several designs of the device are evaluated whether they achieve the design objective.

The cooling device

The cooling device has been developed by the authors (US patent pending). It consists of a rectangular-shaped cooling device with circulating coolant, a heat exchanger, and two pumps. The first pump pushes the coolant (water) from a water reservoir at room temperature. Before the coolant reaches the cooling device, it circulates through a heat exchanger in which heat is transferred from the coolant to ice–water mixture pumped by the second pump. The temperature of the coolant is designed to reach as low as 5°C once it reaches the cooling device. The temperature of the cooling device can vary by adjusting the speed of the ice–water mixture.

The cooling device is then inserted from a small cut made on the neck skin and is placed on the surface of the common carotid artery. The major advantages of this ap-

proach are: (1) the carotid artery is accessible; (2) it is expected that fixing the device inside the neck may not be difficult, since the muscle in the neck is packed tightly; and (3) temperature on the surface of the device can be adjusted and controlled via changing the circulating rate in the heat exchanger.

Mathematical formulation

Unlike in a purely conductive medium, heat transport in perfused tissue is difficult to model because the convective effects of blood flow in tissue are not easily assessed. There are two theoretical approaches currently used to describe the effect of blood flow in a biological tissue. Vascular models represent blood vessels as tubes buried in tissue. When point-to-point temperature non-uniformities are important, vascular model has been proved to be necessary to predict accurately the tissue temperature field. However, because of the complicated vascular geometry, one may only model several large blood vessels individually and neglect the others. On the other hand, continuum models average the effect of blood vessels over a control volume in the region of interest. In the considered tissue region, there is no blood vessel present; however, its effect is treated by adding an additional term in the traditional heat conduction equation for the tissue, as shown in the widely used Pennes bioheat equation (Pennes 1948). In this study, we will use vascular models to simulate the temperature field in the neck region, since the point-to-point temperature variations along the major blood vessels (carotid arteries) are needed to evaluate the effectiveness of the cooling device. In the head region, the Pennes perfusion heat source term will be applied to the heat conduction equation to assess the blood flow effect in the brain.

In this study, a three-dimensional model of the human neck (shown on the left side of Fig. 1) and head (shown on the right side of Fig. 1) is proposed for simulating the temperature fields induced by the cooling device. The vasculature in the neck region is complicated and it consists of several major blood vessels including common carotid arteries, internal carotid arteries, external carotid arteries, and internal and external jugular veins (Edvinsson and MacKenzie 2002). In this study, we only model the common carotid arteries and neglect the other major vessels. Previous studies (Zhu 2000; Bommadevara and Zhu 2002) have suggested negligible vessel-to-vessel thermal interaction among the major vessels located away from each other. Figure 1 gives the schematic diagram of the human neck where the common carotid arteries are modeled as two straight tubes on either side of the neck cylinder. The cooling device, a rectangular column, is placed on the surface of the common carotid artery.

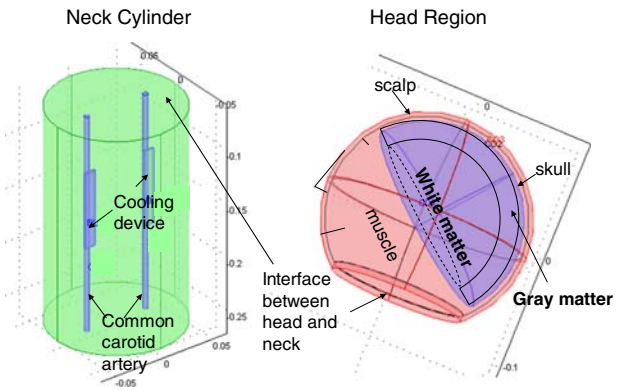

Fig. 1 Schematic diagram of the neck and head regions

A mathematical model is formulated based on the vascular structure shown in Fig. 1. One could write the conservation energy equations for the arteries, and the tissue in cylindrical coordinates as follows:

$$\text{artery}: \rho c\frac{\partial T_{ai}}{\partial t}=k_b\left\{\left[\frac{1}{r_{ai}}\frac{\partial}{\partial r_{ai}}\left(r_{ai}\frac{\partial T_{ai}}{\partial r_{ai}}\right)\right]+\frac{1}{r_{ai}^2}\frac{\partial^2 T_{ai}}{\partial \theta_{ai}^2}+\frac{\partial^2 T_{ai}}{\partial z^2}\right\} - \rho_b c_b u_{ai}\frac{\partial T_{ai}}{\partial z}\quad r_{ai}\le a_{ai}, 0\le z\le L, i=1,2 \qquad (1)$$

$$\text{tissue}: \rho c\frac{\partial T_t}{\partial t}=k_t\left\{\left[\frac{1}{R}\frac{\partial}{\partial R}\left(R\frac{\partial T_t}{\partial R}\right)\right]+\frac{1}{R^2}\frac{\partial^2 T_t}{\partial \theta^2}+\frac{\partial^2 T_t}{\partial z^2}\right\} + \rho_b c_b \omega_n (T_{\text{a,neck}}-T_t)\quad R\le R_t,\ r_{ai}>a_{ai}, \quad 0\le z\le L,\ i=1,2 \qquad (2)$$

where the subscript i denotes the prescribed number of the arteries, subscriptions a, t, n refer to artery, tissue, and neck, respectively, a_{ai} and R_t are the radius of the blood vessel and neck tissue cylinder, respectively, k thermal conductivity, ρ density, c specific heat, and u is the average blood flow velocity in the common carotid artery. Temperature distribution along the carotid artery is determined by heat conduction to the surrounding tissue and to the cooling device (the first term on the right side of Eq. 1) and heat convection due to blood flow (the second term on the right side of Eq. 1). In the neck tissue cylinder, temperature field in the neck is a combination of heat conduction and the blood flow effect in the neck tissue. Local blood perfusion in the neck tissue acts as a heat source to warm the tissue and its strength is directly proportional to the local blood perfusion rate, ω_n (1/s). $T_{\text{a, neck}}$ is the local arterial temperature and is assumed equal to the body temperature of 37°C.

We assume that the neck surface is subject to a room temperature of T_{room} (20°C) and a heat transfer coefficient

h (15 W/m^2 K), which accounts for a combination of natural convection and radiation heat transfer to the surroundings. The effect of the cooling device is modeled as a boundary condition of uniform temperature at the outer surface of the device (T_{cooling} = 5–15°C). The boundary condition at the bottom surface of the cylinder is prescribed as 37°C. The boundary condition at the top surface of the neck cylinder is prescribed as a known heat flux $f(R, \theta)$, which will be determined later via iterations.

Similar to our previous theoretical model of the human head (Zhu and Diao 2001; Diao et al. 2003), the head is modeled as a spherical structure with scalp, bone, muscle, and brain gray and white matter. The detailed geometrical structure of the model is presented in Fig. 1. The blood flow effect in each structure in the head is considered as a Pennes perfusion source term. For any tissue structure (scalp, bone, muscle, gray matter, or white matter), the Pennes bioheat equation is written as

$$\rho c \frac{\partial T}{\partial t} = k_{\text{scalp,bone,muscle,g,w}} \nabla^2 T_{\text{scalp,bone,muscle,g,w}} + \rho_b c_b \omega_{\text{scalp,bone,muscle,g,w}} (T_{\text{bm}} - T_{\text{scalp,bone,muscle,g,w}}) + q_{\text{m}} \quad (3)$$

where q_{m} is the local metabolic heat generation rate, and T_{bm} is the temperature of the arterial blood supplied to the brain tissue. Since the cooling device in the neck reduces the temperature of the blood in the common carotid arteries, it is expected that the blood temperature at the exit of the common carotid artery would be lower than 37°C. In this study, T_{bm} is the average temperature of the common carotid artery calculated from solving for Eqs. 1 and 2.

At the interface between any adjacent layers, temperature and heat flux continuities are required. A convection boundary condition (T_{room} = 20°C, and h = 15 W/m^2 °C) is prescribed at the scalp surface. The bottom boundary surface of the head region is the interface between the head and neck regions. In this study, the boundary condition at the bottom surface is a prescribed temperature distribution $g(R, \theta)$, i.e. determined from solving for Eqs. 1 and 2.

The steady state temperature fields are solved via iterations. Initially, the temperature field of the neck region is solved by assuming an adiabatic boundary condition ($f(R, \theta) = 0$) at the interface. The determined temperature distribution at the interface ($g(R, \theta)$) and the exit temperature of the common carotid artery (T_{bm}) are used as input to solve for the temperature field of the head region. Then, the obtained heat flux distribution at the bottom surface of the head region $f(R, \theta)$ is substituted back to solve for Eqs. 1 and 2. Iterations are continued until the difference between any sequential heat flux $f(R, \theta)$ results in less than 1% change in T_{bm}.

Temperature evolution after the insertion of the cooling device is simulated in both the neck and head regions to evaluate how long it takes to establish the steady state temperature. The initial condition is assumed to be 37°C everywhere. After the steady state temperature fields are obtained, we assume that both $f(R, \theta)$ and $g(R, \theta)$ are unchanged during the transient process. Cooling is penetration from the cold surface of the cooling device to the neck tissue, as well as to the carotid arterial blood. As for the temperature field in the head region, the time-dependent average temperature of the carotid arterial blood at the outlet will be used as input to Eq. 3 to solve for the transient process of heat transfer in the head region.

Temperature fields in the neck, blood vessel and head are solved using finite element method. All the finite element calculations including the mesh generation are performed on FEMLAB 3.1 operated on a Pentium IV processor of 2.79 GHz speed, using 2 GB of memory under a Windows XP SP2 Professional operating system. The numerical model is obtained by applying the Galerkian formulation of Eqs. 1–3. The total number of tetrahedral elements of the finite element mesh in the neck is around 30,000. Mesh independency is checked by increasing the number of elements in the artery by 20% over the current mesh. The finer mesh has induced less than 1% difference in the temperature field. The mesh cannot be further refined since the finer mesh resolution has reached the maximal capacity supported by the internal memory of 2 GB in the computer of our laboratory.

Results

The cooling device is placed in the center of the neck cylinder in the z direction. The baseline design of the device for humans is a rectangular flat sheet (70 mm × 20 mm) with a thickness of 3 mm. The tissue gap between the outer surface of the device and the carotid artery is 0.03 mm. The normal blood flow rate of each common carotid artery, Q, is 240 ml/min. All the physical and physiological properties under normal condition used in the neck and brain model can be found in previous studies (Bommadevera and Zhu 2002; Olsen et al. 1985; Xu et al. 1999) and they are listed in Table 1. Table 2 gives the combination of baseline parameters used in the design and simulation.

Figure 2 has shown that the resulted temperature decay along the common carotid artery is not very sensitive to the iterated value of $f(R, \theta)$. The final converged value of $f(R, \theta)$ is found to be 15.68 W/m^2, which is equivalent to a total of 0.18 W of heat loss from the bottom surface of the head region due to the cooling device in the neck tissue. Most of the cooling of the arterial blood occurs in the vicinity of the

Table 1 Physical and physiological properties under normal conditions

Parameter	Specific heat, C (W/kg°C)	Mass density, ρ (kg/m^3)	Thermal conductivity, k (W/m°C)	Perfusion rate, ω (1/s) or (ml/min per 100 g)	Metabolic rate, q_m (W/m^3)	Radius, R (mm)
Blood	3,800[a]	1,050[c]	0.5[c]	–	–	2.5
Neck	3,700[b]	1,050[c]	0.5[c]	0.000167 (1.0)[a]	180.2[a]	60
Head muscle	3,700[a]	1,050[c]	0.5[c]	0.000167 (1.0)[a]	180.2[a]	–
Scalp	4,000[a]	1,000[c]	0.34[c]	0.000334 (2.0)[a]	363.4[a]	93
Bone	2,300[a]	1,500[c]	1.16[c]	0.0003 (1.8)[a]	368.3[a]	89
Gray matter	3,700[a]	1,050[c]	0.5[c]	0.01333 (80)[a]	10,854[a]	85
White matter	3,700[a]	1,050[c]	0.5[c]	0.00333 (20)[a]	5,725[a]	67

[a] Xu et al. (1999)

[b] Bommadevera and Zhu (2002)

[c] Olsen et al. (1985)

Table 2 Parameters of the baseline design

Cooling device	Geometry	70 mm long × 20 mm wide × 3 mm thick
	Location in neck	0.03 mm from the carotid artery
	Surface temperature	5°C at the outer surface of the device
Neck cylinder	Geometry	120 mm in diameter and 200 mm long
Carotid artery	Geometry	2.5 mm in diameter and 200 mm long
	Location in neck	30 mm away from the center of the neck cylinder
	Flow rate	240 ml/min in each carotid artery

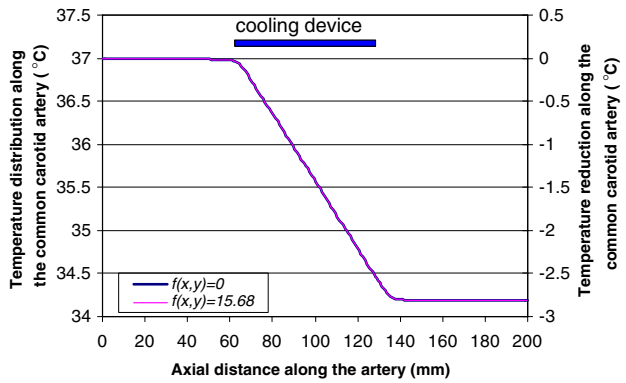

Fig. 2 Sensitivity of the simulated temperature decay along the carotid artery to the iterations of the boundary condition at the interface

cooling device along the blood vessel. The temperature decay along common carotid artery, ΔT, is approximately 2.82°C. The total heat transfer from both common carotid arteries can be calculated by $q_{loss} = 2\,\rho CQ\Delta T$, where ρ is blood density and C is specific heat of blood. The current design of the device results in 90 W of heat transferred

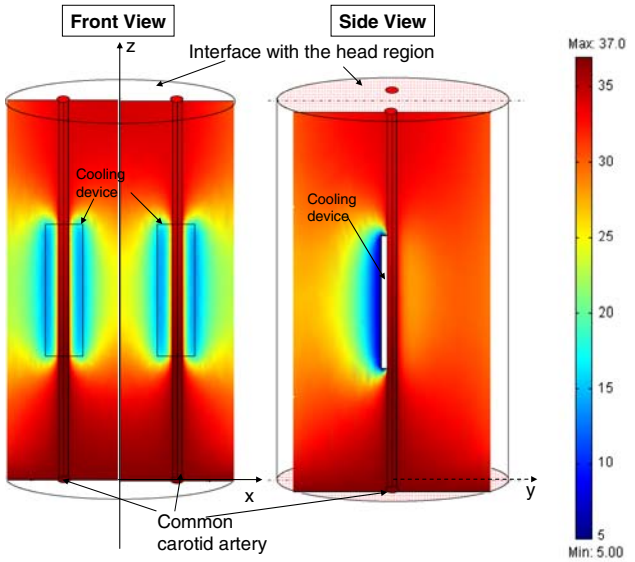

Fig. 3 Temperature contours in the neck region. **a** In a plane perpendicular to the cooling device; **b** in a plane parallel to the cooling device. Temperature on the surface of the cooling device is 5°C, while temperature along the common carotid artery varies from 37°C at its entrance to 34.2°C at its exit. All parameters used are listed in Tables 1 and 2

from both the common carotid arteries. The total heat loss due to the cooling device from the head region is therefore, 90.18 W.

Temperature contours in both the neck and head regions are given in Figs. 3 and 4. Note the different temperature scales in the two figures. The temperature fields of two planes are presented in Fig. 3, in which the geometrical location of the cooling device can be identified. The isotherm in the neck moves from 5°C on the device surface (blue) to 25°C in the neck tissue (yellow), and finally to 35°C inside the carotid artery (red). The temperature decay along the common carotid artery is approximately 2.8°C.

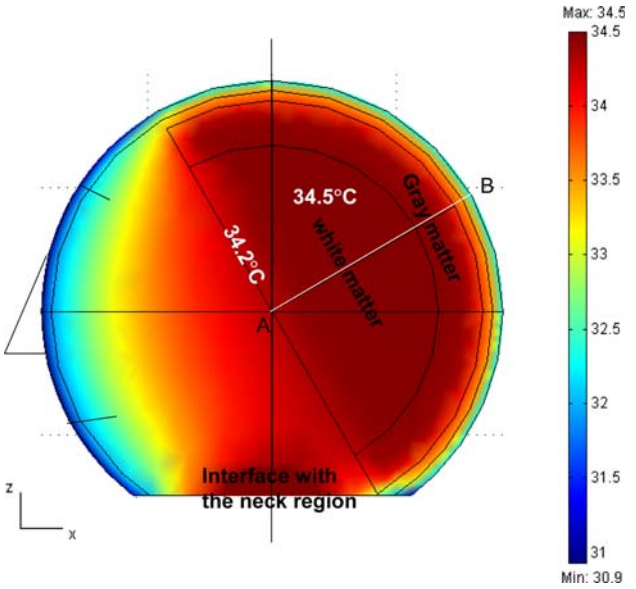

Fig. 4 Temperature contours in the head region. The hemisphere represents brain tissue consisting of *white* matter (the *inner* hemisphere) and *gray* matter (the *hemispherical* shell). Temperatures in the brain tissue are relatively uniform (around 34.5°C). The surface temperature of the scalp is around 32°C. All parameters used are listed in Tables 1 and 2

Similar to the results of a previous study by the authors (Zhu and Diao 2001), the brain tissue consisting of the white and gray matter is cooled almost uniformly by 2.8°C (from normal 37.3 to 34.5°C). The bottom surface of the head region is significantly cooled due to the cooling device in the neck. The temperature on the superficial area of the brain tissue is reduced to as low as 34.2°C. The current design of the cooling device, thus, satisfies the design requirement of lowering the brain tissue temperature by 2.0°C.

Parametric studies are carried out to test the sensitivity of the simulated temperature field to various design parameters. These parameters include the tissue gap between the cooling device and artery, its length and width of the cooling device, the surface temperature of the device, the blood perfusion in the neck muscle, and the flow rate of the common carotid artery.

Figure 5 illustrates the temperature decay along the common carotid artery with different gaps between the device and artery. The simulation shows a temperature drop of 2.8°C at the outlet of the common carotid artery when the device touches the blood vessel. Conduction resistance between the device and artery is critical in determining the cooling ability of the device to the arterial blood. Cooling along the carotid artery is greatly decreased when the device is placed far away from the blood vessel.

Temperature decay along the common carotid artery occurs primarily in the vicinity of the cooling device.

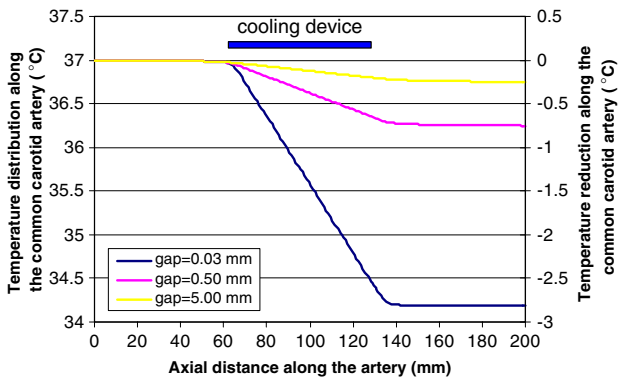

Fig. 5 Effect of the tissue gap between the device and carotid artery on the temperature distribution (*left y* axis) and temperature reduction (*right y* axis) along the common carotid artery. The *bar* illustrates the axial location of the device

Figure 6 examines the cooling along the center of the artery with different lengths of the device. Temperature drop could be as low as 3.9°C when the device is 10 mm long, while it decreases by 44% when the length is halved (5 mm, 2.2°C). The design of a shorter device still satisfies the design requirement and is less intrusive. On the other hand, the simulated results show that the temperature decay is not sensitive to the width of the device.

In theory the lower the surface temperature of the device, the larger the temperature decay along the arterial cooling. Clinicians do not recommend the interstitial cooling below the freezing temperature of 0°C because of potential tissue damage to the surrounding jugular veins and nerves. The sensitivity of the cooling capacity of the device to the device temperature is illustrated in Fig. 7. Even at a higher surface temperature of the device at 10°C, the temperature reduction (2.3°C) along the common carotid artery is still larger than that required by the design goal.

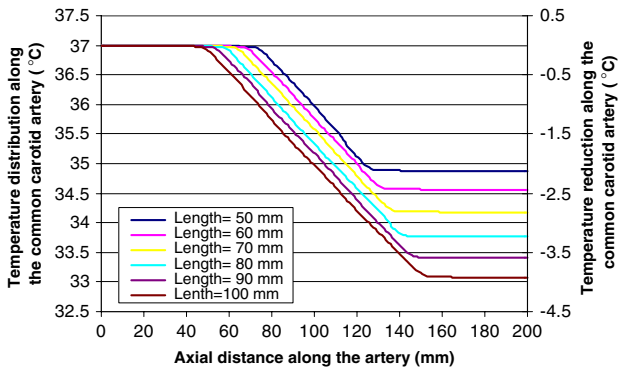

Fig. 6 Effect of the length of the device on the temperature distribution (*left y* axis) and temperature reduction (*right y* axis) along the common carotid artery

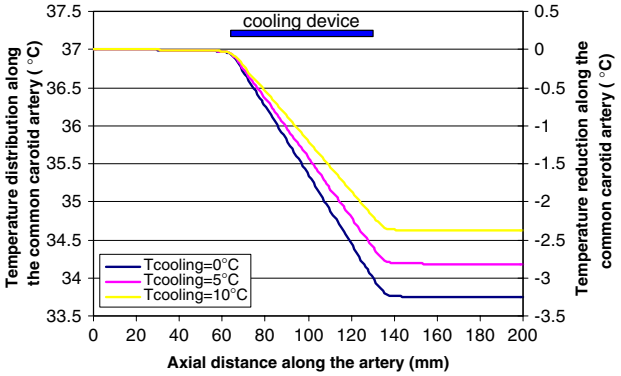

Fig. 7 Effect of the coolant temperature of the device on the temperature distribution (*left y* axis) and temperature reduction (*right y* axis) along the common carotid artery

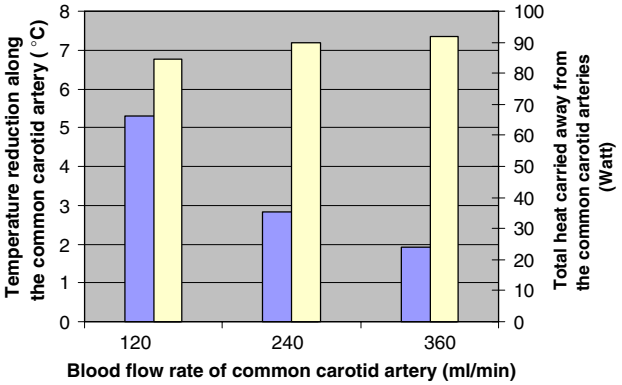

Fig. 9 Effect of the blood flow rate of the common carotid artery on the calculated temperature reduction along the common carotid artery (*left y* axis and *blue bars*) and total heat carried away from the carotid arterial blood (*right y* axis and *yellow bars*)

Only the common carotid arteries are modeled individually in the neck cylinder. The rest of blood vessels in the neck are considered as a Pennes perfusion source term as shown in Eq. 2. The normal blood perfusion rate in the neck muscle is around 0.000334 (1/s), equivalent to 2 ml/min per 100 g tissue. It is expected that vasoconstriction may occur after the cooling in the neck by the device. Our simulated results suggest that the temperature decay along the carotid artery is not sensitive to the change of the local blood perfusion rate in the neck, as shown in Fig. 8.

It is well known that blood flow rate (Q) in a blood vessel affects the thermal interaction between the temperature decay along its axial direction and surrounding tissue. In this study we evaluate the effect of the blood flow rate of the common carotid artery on the axial temperature decay along the vessel, as shown in Fig. 9. The blue bars represent the temperature reduction along the common carotid artery, ΔT, while the yellow bars represent the total heat carried away from the arterial blood using equation $q_{\text{loss}} = 2\rho CQ\Delta T$. As expected, doubling the blood flow rate in the common carotid artery would decrease the temperature drop by almost 50% ($\Delta T = 5.3$°C when $Q = 120$ ml/min vs. $\Delta T = 2.8$°C when $Q = 240$ ml/min), while decreasing the blood flow rate by half would double the temperature drop. The temperature drop along the common carotid artery is almost inversely proportional to its blood flow rate. However, since the heat transfer rate q_{loss} is proportional to the multiplication of the temperature reduction and blood flow rate, $Q\Delta T$, the heat loss from the common carotid artery only changes slightly from 90 W ($Q = 240$ ml/min) and it varies between 84 W ($Q = 120$ ml/min) and 92 W ($Q = 360$ ml/min).

The evolution of the cooling process is evaluated in Fig. 10, which gives the temperature distribution along the common carotid artery as a function of time. In this study the characteristic time t_c of the transient process is defined as

$$\frac{T(r,\theta,\phi,t_c) - T(r,\theta,\phi,0)}{T_c(r,\theta,\phi) - T(r,\theta,\phi,0)} = 99\%, \tag{4}$$

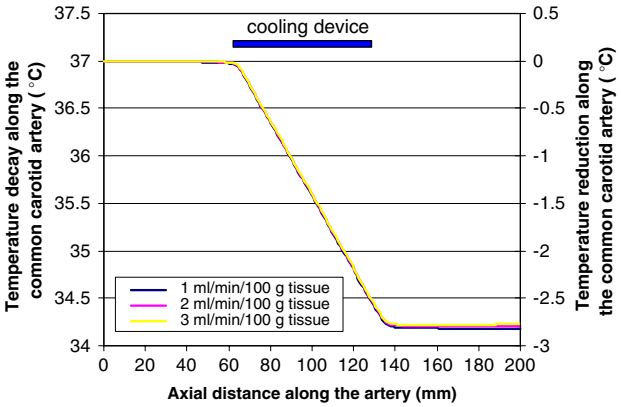

Fig. 8 Effect of the local blood perfusion rate in the neck muscle on the temperature distribution (*left* y axis) and temperature reduction (*right y* axis) along the common carotid artery

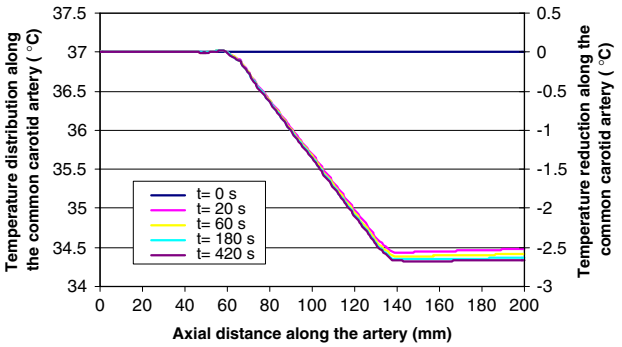

Fig. 10 Transient temperature profiles along the common carotid artery responding to cooling. Initially the temperature along the artery is uniform as 37°C

where T is temperature anywhere in the simulated domain, and T_c is the steady state temperature. It takes less than 7 min for the outlet temperature of the common carotid artery to reach its steady state. After the time-dependent temperature of the arterial blood is substituted into Eq. 3, the change of the temperature field in the head region is simulated. In Fig. 11, the radial temperature distribution along line A–B in Fig. 4 is plotted as a function of time. The temperature profile along the line is very close to the steady state temperature profile only after 30 min, while the characteristic time for most region of the brain tissue based on Eq. 4 is calculated less than 60 min.

Discussion

There are several limitations associated with the theoretical model due to the restriction of the computer software used in the study. One is the assumption of a uniform initial condition for the transient process, while realistic temperature fields in the neck and head have shown a lower temperature (<37°C) in the superficial layers of the regions. Previous theoretical analysis by the authors (Diao et al. 2003) has suggested that a realistic initial condition would result in a shorter time duration to establish a steady state temperature field than the current prediction. Therefore, our calculated result can be viewed as the upper limit of the characteristic time. A more realistic characteristic time, which is shorter than 60 min predicted by the study, fits the clinically acceptable treatment window of 1–2 h during which brain hypothermia must be initiated to confer any significant neuro-protection. The other limitation is the assumption that both the functions $f(r, \theta)$ and $g(r, \theta)$ are kept unchanged during the transient temperature simulation. We believe that both functions should affect the transient process, however, their effects on the temperature decay along the carotid artery and temperature field within the brain hemisphere are very small. Based on the calculation, the heat transfer rate from the interface is only 0.18 W, which is a very small value in comparison with that due to the temperature reduction along the carotid artery of 90 W. The dominant factors of the transient process along the carotid artery and the brain hemisphere are the small conduction resistance between the device and blood vessel, as well as the temperature of the arterial blood supplying the brain tissue. The two limitations can be addressed in the future when additional computational resources are available.

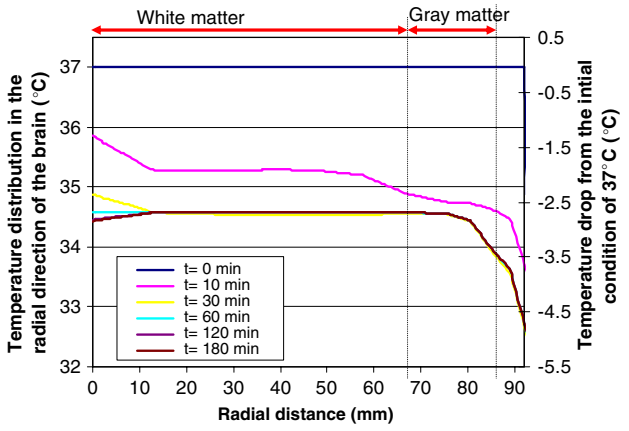

Fig. 11 Simulated temperature changes in the radial direction of the brain hemisphere at various time instants. *Double arrows* represent the regions of the *white* and *gray* matter, respectively

It is known that the total blood flow rate in both common carotid arteries represents approximately 80% of the blood supplied to the brain. The other 20% comes from the vertebrate artery. In the normal condition, human brain has the mechanism of auto-regulation to ensure stable blood supply to the brain tissue. In the majority of the stroke patients, it is ischemic in nature. One would expect to see a decreased blood flow rate in either the common carotid artery or the vertebrate artery. However, blood flow response to cooling is more complicated. Most previous clinical and animal studies have shown local or global decrease in blood perfusion in brain during whole body or selective brain cooling (Busija and Leffler 1987; Diao and Zhu 2006; Okubo et al. 2001). It is speculated that this is a direct result of the coupling between the local blood perfusion and local metabolism, that usually decreases as local temperature drops. However, the coupling relationship may be disrupted by stroke or head injury. In some clinical studies blood perfusion rate actually increases during cooling (Kuluz et al. 1993). A study of cooling response of carotid artery segments has shown vaso-dilation after cooling (Mustafa and Thulesius 2002). It is still not clear whether this kind of response can be applied to smaller arterioles, which have been considered as the dominant component of the vascular tree in determining the total flow resistance. In the current theoretical simulation, it has shown that the temperature reduction along the common carotid artery is almost inversely proportional to the blood flow rate. If the blood flow rate is indeed reduced due to the interstitial cooling device, temperature decay along the artery will be as high as 5.3°C as simulated by the model, while increasing Q to 360 ml/min results in a temperature reduction of 1.9°C. However, one thing needed to be pointed out is that the total heat loss from the arterial blood to the cooling device is not very sensitive to the flow rate. In another word, the cooling capacity of the device varies slightly between 84 and 92 W for the possible range of the blood flow rate responding to cooling.

The currently available non-invasive cooling approaches usually require a long time to establish a steady state

(whole body cooling), induce non-uniform temperature distribution in the brain tissue (head helmet), or is ineffective (neck collar). The powerful and effective approaches such as vena-venous extracorporeal device (Dae et al. 2003; Georgiadis et al. 2001) and intra-parenchymal brain cooling probe (Zhu and Rosengart 2007) are all associated with invasive surgical procedures. The major advantages of the developed cooling device include its small size, powerful cooling capacity, fast cooling capability, and possible control of the rewarming rate. It can be used in conjunction with other cooling approaches, including using a cooling helmet or nasal cooling, to maximize neuro-protection. A more detailed and complicated theoretical model can be developed in the future to simulate both mass and heat transport in tissue and provide guidance for treatment protocols.

Although targeted brain hypothermia is proposed to avoid well-documented systemic complications induced by whole body cooling, cooling the brain along may still affect overall thermoregulation in patients. It may change the body heat balance. The jugular veins carrying the cold blood away from the head region may induce a drop in the body core temperature, unless the rest of the body temperature is actively maintained. Lowering the brain temperature may also result in confusion in the hypothalamus region, which may regulate the body to increase heat conservation. The final decision should be made by physicians whether the benefits of a cooling approach outweigh its risks based on the patient's conditions. Currently, a prototype of the device has been developed and has been used in animal studies in our laboratory to evaluate the performance of the device in a biological environment. Future investigation may include studies on autopsy specimens for an optimized and safe placement of the cooling device and theoretical simulation of a more realistic vascular geometry in the neck and head regions.

The current device also has the potential to control fever in stroke patients. Brain-injured patients exhibit body temperature elevations during acute and subacute recovery phases. Castillo et al. (1998) stated that 60% of 260 patients with acute hemispheric infarction developed hyperthermia (axillary temperature > 37.5°C) within 72 h of hospital admission. Reith et al. (1996) studied 390 prospective stroke patients and found that, independent of stroke severity on admission, the relative risk for death and worse functional outcome increased by a factor of 2.2 for each degree Celsius increase in body temperature. Many investigations have suggested that maintaining euthermic body temperature (near 37°C) throughout hospitalization is a logical step toward improvement of outcome. The current device may contribute to fever control via two mechanisms. One is the direct cooling of the arterial blood. A 2.8°C temperature drop can be achieved within 60 min based on our simulation. The actual time required may be shorter than 60 min due to the cooled venous blood collected by the jugular veins. It is well known that 20% of cardiac output is supplied to the brain tissue. The cooled arterial blood provides nutrients to the brain tissue and is later collected by the jugular veins and flowing back to the heart. The cold blood will mix with the warm blood collected from the rest of the body and has the potential of eliminating fever in stroke patients.

Brain hypothermia has been demonstrated beneficial not only to stroke or head injury patients, but also to patients undergoing open heart or neck surgeries. Most of the current commercial devices in market are neck collar or head helmet. Large thermal resistance of the neck muscle result in ineffectiveness of those devices when fast cooling is critical to the patient's outcome. Clinical studies have shown the cerebral benefits of lowering brain temperature prior to complicated surgeries (such as cardiac arrest and aortic repair) and/or during the operative procedures (such as carotid endarterectomy and resection of extra-cranial aneurysm). In most of these clinical applications, the common and internal carotid arteries are routinely exposed as part of the surgical procedures, so that placing the developed cooling device would not add additional risk to the patient. The cooling device could easily be incorporated into these invasive surgical procedures to achieve rapid brain hypothermia prior to or during the surgical repair. Assuming that the benefit of our approach outweighs its risk, we envision this study to be the first step to develop a reliable cooling device that is anticipated to find broad use in various clinical applications and to potentially benefit a large patient population.

In summary, the feasibility of the developed cooling device is evaluated using a theoretical simulation of the temperature fields in the neck and head region in humans. The length of the device, the temperature of the device, and the tissue gap between the device and the blood vessel are the dominant factors that determine the effectiveness of this cooling approach. Under the current design parameters, the device is capable of inducing 2.82°C temperature drop along the common carotid artery and 90 W of heat carried away from the arterial blood and up to 3.1°C temperature reduction in the brain tissue. Brain hypothermia can be achieved within one hour under the current design. The geometrical and thermal parameters of the device can be modified so that the device would be more compact to induce less damage to the surrounding structures in the neck while it still satisfies the design requirement of the targeted brain hypothermia.

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