Modeling brain cooling treatment approved for hypoxic-ischemic encephalopathy in infants to treat stroke and cardiac arrest in adult patients

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1. Executive Summary

Brain cooling or induced hypothermia have been shown to be effective modes of neuro-protection during hypoxic insult in newborn infants. It is believed that hypothermia helps prolong neuronal survival by reducing damage from excitotoxins, inflammation, free radicals, and necrosis. However, such treatment for hypoxia resulting from heart attack or stroke in adults has not shown consistent experimental efficacy. To investigate this discrepancy, we modeled the transient and steady-state heat transfer that occurs during brain cooling using an external cap in infants and adults using COMSOL. The infant model provided insights into the mechanism of induced hypothermia in treating hypoxia. In particular, it was established that only partial cooling of the gray matter is necessary for therapeutic effects. By comparison, the adult model showed over two times less penetration of neuro-protective cooling into the gray matter brain tissue. It was reasoned based on analysis of the two models that the larger volume and perfusion rate in the adult head were responsible for the non-uniform outcomes, making brain cooling an ineffective method of treating adults.

2. Introduction

2a. Background

Brain cooling has been shown to be successful in diminishing the extent of brain injury resulting from hypoxia.[16] For victims of near-drowning, neurological recovery is possible if hypothermia is induced soon after the insult.[19,20] Several studies point to the possibility of using surface or endovascular cooling in patients who have suffered a hypoxic insult.[1,4,7,9,11,13] For example, in infants with hypoxic-ischemic encephalopathy (HIE), a condition in which insufficient amounts of oxygen are supplied to the brain causing neuron apoptosis, hypothermia of the brain via a cooling device (CoolCap ®) has been approved by the FDA and used successfully to mitigate neurological damage.[14]

HIE is a significant cause of death in newborn infants worldwide, with an incidence between 1.8 and 6 per 1000 term infants in developed countries, and a much higher incidence in developing countries.[16] The condition can be brought on by a variety of causes, including complications during birth, blocked blood vessels, drowning, and drug overdose. HIE in neonates is a progressive process that begins with an initial hypoxic-ischemic event, also known as the primary phase of energy failure. After resuscitation from this event, there is a latent stage where cerebral oxidative metabolism is restored. However, a secondary phase of energy failure occurs 6 to 24 hours later, which causes further deterioration in the brain. The window for treatment occurs between these primary and secondary energy failures, meaning a significant cooling of 3-4 ^{o}C needs to be obtained within six hours to offer protection. This temperature drop range has been confirmed in animal studies[2,12] and clinical trials[6] leading to the development of the CoolCap. Long term effects of HIE can include mental retardation, seizures, cerebral palsy, and death. Hypothermia may prevent this by mitigating the delayed energy failure, reducing nitric oxide production, and blocking specific biochemical cascades that lead to brain cell apoptosis.

These effects of HIE are similar to many disease states brought on by sudden acute hypoxia (Figure 1). For example, in a stroke, the lack of blood flow creates hypoxic conditions that can quickly induce apoptosis leading to permanent brain damage. Similarly, in a heart attack, failure of the heart to provide blood to the brain can lead to apoptosis. Thus, it is plausible that if the adult brain was cooled soon after such an insult, cell cytotoxicity could be reduced as it is in infant HIE patients. Some studies have already suggested that hypothermia in the brain is a potential treatment for adults suffering from stroke or cardiac arrest.[1,4,9,11] However, the CoolCap is currently only approved for use on newborns.

2b. Design Goals

This project has two major goals: to validate the use of the CoolCap for treating infants and to investigate whether a similar device could offer neuro-protective cooling to adults who have suffered a stroke or cardiac arrest.

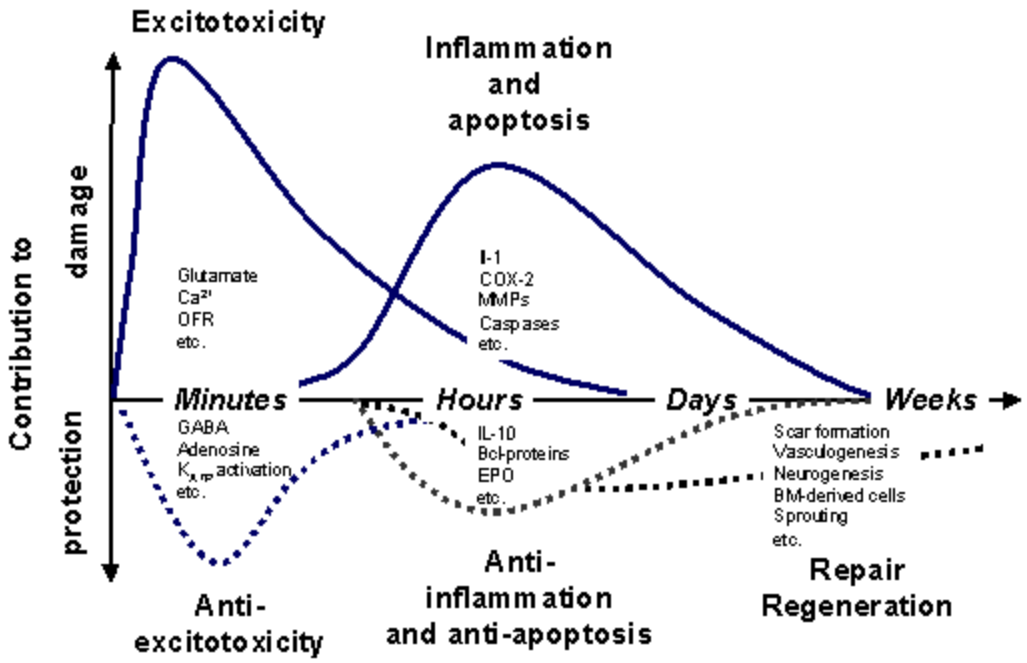


Figure 1: The pathological progression of generalized neural ischemia.[22] HIE, stroke, and heart attack can all lead to neural damage through two phases. First, excitotoxicity causes necrosis within minutes. This is followed by a second phase of apoptosis taking place 6-72 hours after hypoxic insult. Brain cooling in infants with HIE protects against this second phase.

Analytical and numerical methods are used to model the temperature of the brain over time during application of a selective head cooling apparatus containing water maintained at 10 °C. We will compare the temperature behavior in an infant and an adult undergoing the same treatment, and by comparison of the two determine if sufficient cooling has occurred in the adult to slow the destructive neurological processes that result in neural hypoxia. Similar results in infant and adult models would signal that a comparable cooling treatment is plausible for adults. These results could be helpful to those who are designing methods of therapeutic hypothermia for stroke and cardiac arrest patients, as well as to physicians who are considering the use of therapeutic hypothermia in the care of such patients.

Several animal studies have shown that the most effective temperature range for neuro-protection is between 32 and 35^{o}C [(2,12)]. Clinical trials conducted on infants confirmed these results.[(6)] Based on these studies, and considering the fact that the CoolCap System [(14)] approved by the FDA for treating infants with HIE specifies a temperature decrease to 34-35^{o}C, we seek a temperature drop of approximately 3^{o}C in the brain tissue of infants (from an assumed body temperature of 37^{o}C) for validating the use of a cooling cap as an effective treatment of HIE. Similarly, we look for a comparable temperature drop in adult models, to make initial claims of the validity of such a treatment for stroke and cardiac arrest patients.

3. Simplified Analytical Solution for Infant

3a. Methods and Results

An introductory study was conducted to assess the approximate temperature response within the brain from a cooling cap. To obtain an analytical solution of the steady-state temperature profile of a cooled brain, an infant head was modeled as a hemisphere with constant temperature boundaries (Figure 2). Considering only conduction, this geometry can be simplified into a one-dimensional problem along the radially symmetric line from r = 0 to r = R, where the radius is assumed to be 6 cm. Assuming steady-state with no convection or heat generation, equation 1 can be solved for the temperature profile of the brain. The result is presented in equation 2 using the boundary conditions that the temperature at r = 0 is 37°C and the temperature at r = R is 10°C. The resulting hyperbolic curve is plotted in Figure 3. Details that led to the arrival of this solution are shown in Appendix B.

$$\left(\frac{\mathrm{k}}{\mathrm{r}^2}\right) * \left(\frac{\mathrm{d}}{\mathrm{dr}}\right)\left[r^2 * \frac{dT}{dr}\right] = 0 \qquad (1)$$

$$T = \frac{2.7458}{r} + 9.542 \qquad (2)$$

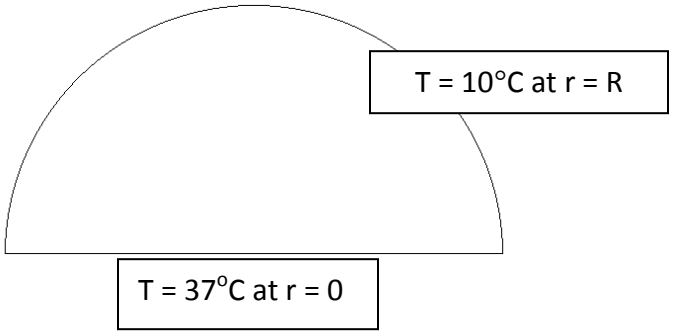


Figure 2: The geometry for a simplified analytical solution. At the center of the circle, the temperature is the body temperature of 37°C. At the surface, a cooling device is modeled by a constant temperature of 10°C.

3b. Discussion

The solution to equation 1 results in a hyperbolic temperature profile from the head surface to the center of the brain (Figure 3). However, a number of assumptions were made that make this profile unrealistic. The heat transfer equation was simplified to only include

conduction, whereas convection and perfusion would also play a role in a real brain. The temperature at the core (r = 0) was assumed to stay constant at 37 °C, while the temperature at the surface (r = R) was constant at 10 °C, which again is an unrealistic assumption. Since the geometry was assumed to be a homogenous hemisphere with constant heat transfer properties, it fails to account for different regions of the head and the brain. Further implementation in COMSOL is therefore necessary for all of these assumptions to be addressed.

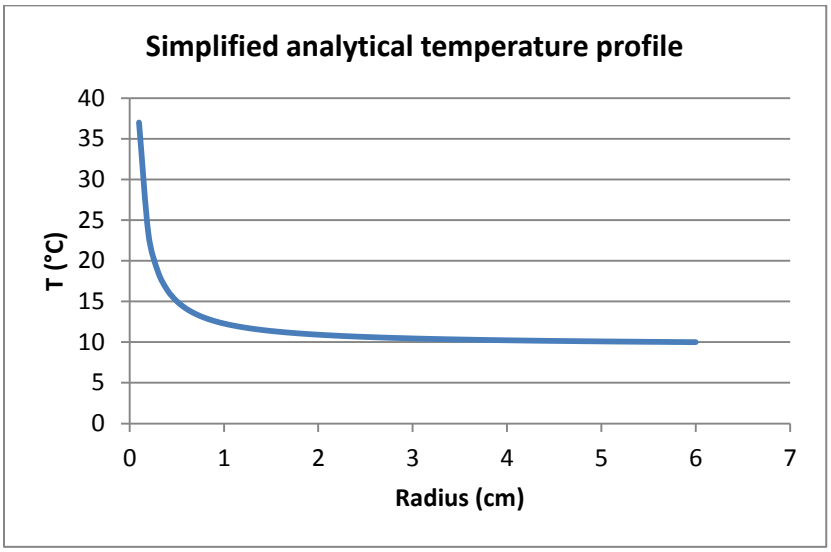


Figure 3: A simplified analytical solution for an infant's head during surface cooling, assuming only conduction. The cooling device is applied at a radius of 6 cm. Significant cooling penetrates almost to the core of the brain.

4. COMSOL Implementation: Infant Model

4a. Model Development

Due to the shortcomings of the analytical solution, a COMSOL model was built to verify the significant brain temperature drop during surface cooling on an infant head. An axisymmetric layered hemisphere was used to model the brain and head where the cooling takes place (Figure 4). The head layers included the scalp, bone, gray matter brain tissue, and white matter brain tissue. Differentiation into these layers reflected the varying material properties and perfusion constants throughout the head, providing a more physically realistic solution compared to the analytical model.

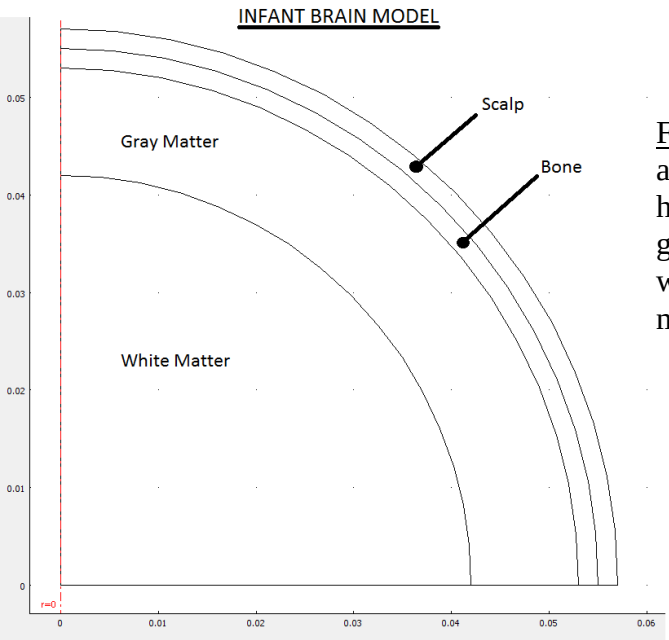


Figure 4: The infant head and brain was modeled as concentric layers of an axisymmetric hemisphere. The layers included the scalp, bone, gray matter, and white matter. Axial symmetry was specified about the vertical axis. Axes markings are in meters.

Within each layer, the 2D-axisymmetric heat transfer equation was solved under transient conditions (equation 3). This equation assumed no convection, and instead included a perfusion term from the Pennes bioheat equation to account for blood flow, along with a heat generation term, Q, to account for metabolic heat generation. Perfusion and metabolic heat generation were included in all four layers.

$$\rho C_p \frac{\delta T}{\delta t} = k \frac{1}{r^2} \frac{\delta}{\delta r}\left(r^2 \frac{\delta T}{\delta r}\right) + \frac{\rho c \dot{V}(T_a - T)}{Vol} + Q \qquad (3)$$

Equation (3) was solved using the following boundary conditions: insulation along the horizontal axis, symmetry along the vertical axis, and constant temperature of 10°C along the head surface. A constant temperature was used because the CoolCap circulates temperature-controlled water through the cap to cool the brain. The initial condition assumed was that the entire head starts at 37°C. The model parameters used for material properties, perfusion, and metabolic heat generation used in each layer are shown in Appendix A.

A triangular mesh was generated by specifying the maximum element size in all four domains. Mesh convergence was tested to ensure a mesh-independent solution by measuring the temperature in the scalp at the point (0.034, 0.0444) after 5 seconds. Convergence was achieved when the maximum element size was specified as 0.0005, which created a 43937 element mesh (Figure 5).

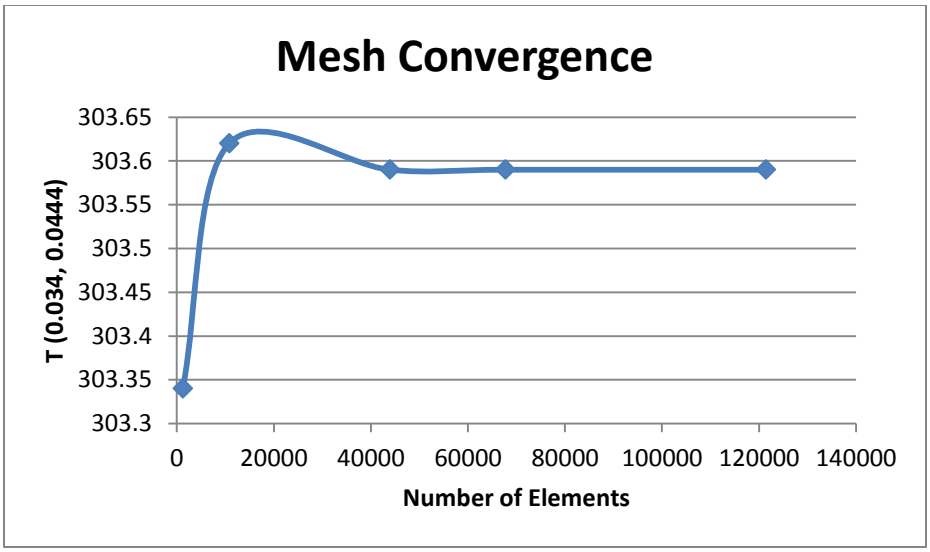
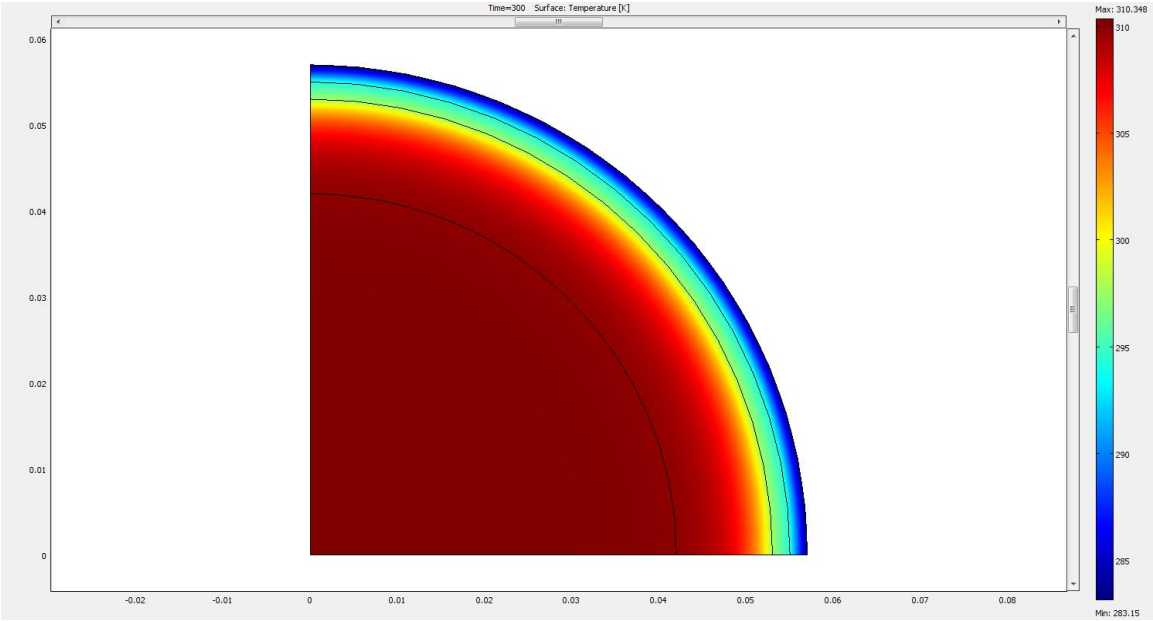


Figure 5: Mesh convergence was tested by measuring the temperature in the scalp at the point (0.034, 0.0444) after 5 seconds to ensure a mesh-independent solution. Convergence was achieved using a maximum triangular element size of 0.0005 in all domains.

4b. Results

A temperature profile of the infant head after five minutes of application of the cooling device is shown in Figure 6. Qualitatively, it can be seen that the innermost region of the brain- the white matter- has not cooled. Cooling penetrates partly into the gray matter only. A steady temperature was reached in all layers of the infant model after approximately five minutes of application of the cooling cap (Figure 7). The infant model showed rapid cooling in the outer layers of the head and more gradual cooling in the gray matter brain tissue. The scalp temperature approached the temperature of the CoolCap due to its small thickness and proximity to the cap. The bone equilibrated to approximately 20^{o}C and buffered much of the heat transfer due to the blood perfusion and low heat capacity of the layer.



$37^{o}C$

$10^{o}C$

Figure 6: Temperature profile of the infant brain model after five minutes. The profile did not change after five minutes as the temperature in all the regions reached steady state.

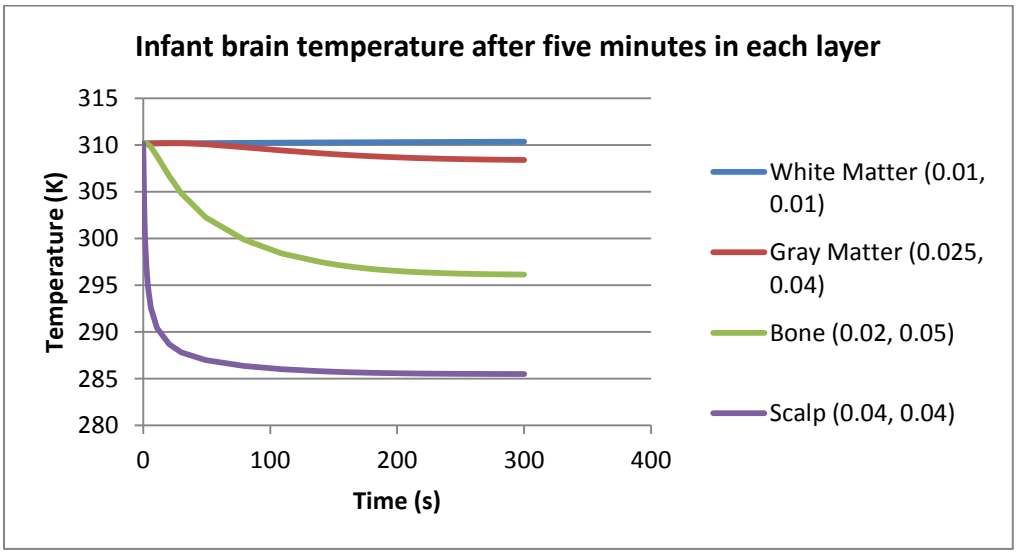


Figure 7: After 5 minutes of application, the head layers of the infant model are approaching steady state. Cooling penetrates only into the gray matter. The white matter remains at the initial temperature.

To quantify the cooling occurring in the gray matter, the extent of cooling therapy is illustrated in Figure 8, showing the steady state profile of the infant head after six hours of application. As it has been shown extensively in literature [2,6,12,14] that at least a 3°C temperature drop is desirable and necessary for hypothermia to take place and yield therapeutic results, we set a 3°C threshold to analyze how much cooling has occurred. Cooling of over 3°C below body temperature penetrates approximately 10 mm into the surface of the head. Given that these first four millimeters are scalp and bone, this correlates to significant cooling penetrating 6 mm into the gray matter layer, which is about halfway. We calculate that this is approximately 51% by volume of the gray matter cooled below the desired 3°C.

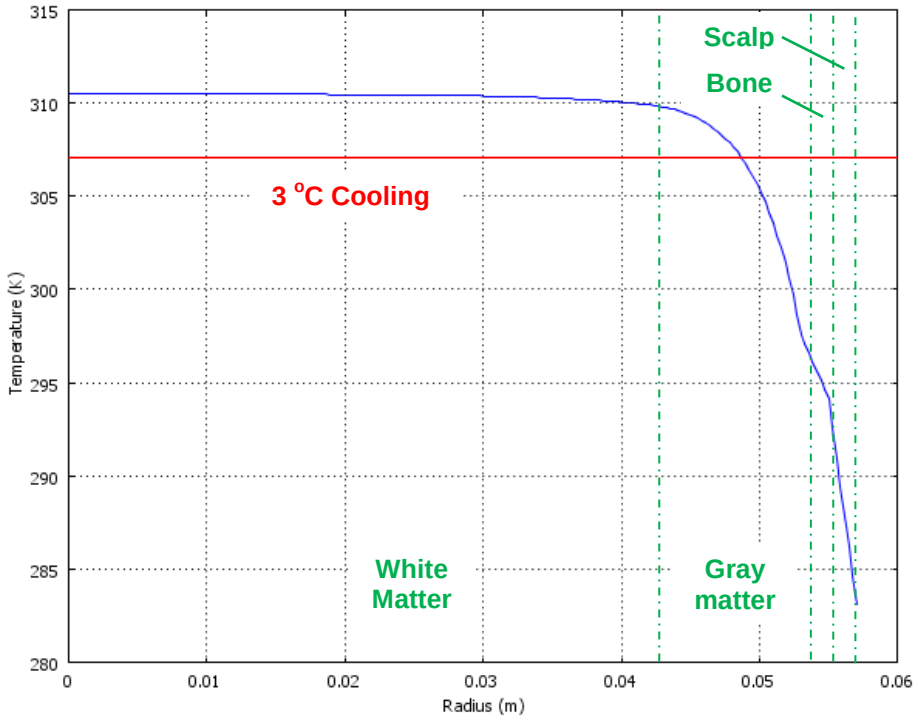


Figure 8: Steady-state temperature profile of the infant brain, viewed after six hours of cool cap application. Cooling penetrates approximately halfway into the gray matter. No penetration in the white matter is observed.

4c. Discussion

Results from the infant model show that steady state was reached quickly (< 5 min) and that therapeutic cooling penetrated about halfway into the gray matter layer (5-6 mm). However, the white matter did not show any significant cooling, even after six hours of application. The combination of heat fluxes contributing to steady state are due to the surface cooling, metabolic heat generation, and perfusion. At steady state, the heat flux out of the head and into the cool

cap matches the heat flux produced in the head from metabolism and perfusion. The large perfusion in the gray matter thus prevents cooling from penetrating further into the brain. Comparing our results to literature studies [12,14] we find that literature results suggest that surface cooling is therapeutic for infants with HIE. As we only observe partial cooling of the brain below the commonly set threshold of 3°C, we conclude that partial hypothermia of the brain is sufficient to prevent damage mechanisms from taking place, or alternatively, that these mechanisms occur only in the gray matter and thus the observed cooling of the gray matter is sufficient for therapeutic effects. These conclusions may be vital in understanding how HIE inhibits normal function and in what ways hypothermia aids therapy. Furthermore, the validation of the FDA approved CoolCap device motivates the following investigation of brain cooling using a similar device in adults who have suffered hypoxic neural insult.

4d. *Comparison with Analytical Solution*

The COMSOL model of the infant brain had large discrepancies in relation to the simplified solution. Unlike the computer model, the simplified solution lacked the crucial perfusion term, which, according to the COMSOL model, is largely responsible for the stability of brain temperature over extended periods of time. Instead it showed a sharp decrease in temperature everywhere, but the inner core of the brain. This inaccuracy exemplifies the tissues' variation from a slab model. Therefore a more intricate computer simulation is required to achieve results similar to those found in experiments, not seen in simplified analytical models.

5. COMSOL Implementation: Adult Model

5a. Model Development

The adult model shown in Figure 9 is similar in design to that of an infant, both being modeled as quarter spheres around an axisymmetric y-axis. The most notable difference is the larger volume and thickness of the brain, due to a more developed body. Additionally, the adult model is characterized by larger perfusion rates in all the layers, as a result of a larger head with a more extended network of capillaries. These vessels are capable of transporting a greater volume of blood to and from the head.

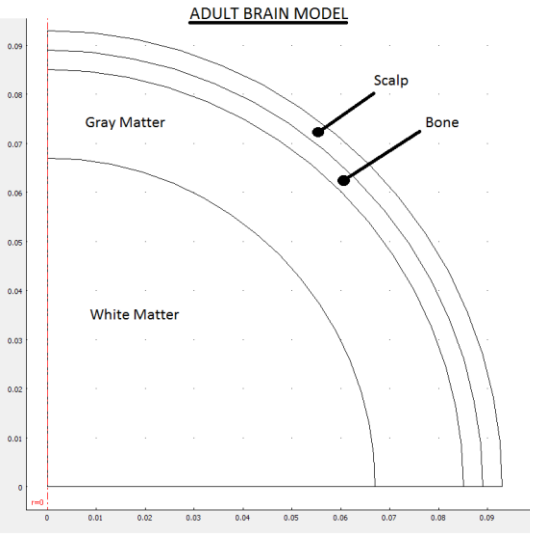


Figure 9: Schematic of the adult model in COMSOL. Blood perfusion and metabolic heat production are incorporated within each layer. The boundary conditions were symmetry along the vertical axis, insulation along the horizontal axis, and a constant temperature at 10°C along the surface.

5b. Results

The adult model showed less cooling overall than the infant model due to a larger head volume and a higher perfusion rate in all layers. The temperature profile is shown in Figure 10. Significant cooling was achieved in the scalp and bone layers, but only the outermost couple of millimeters of the gray matter were cooled.

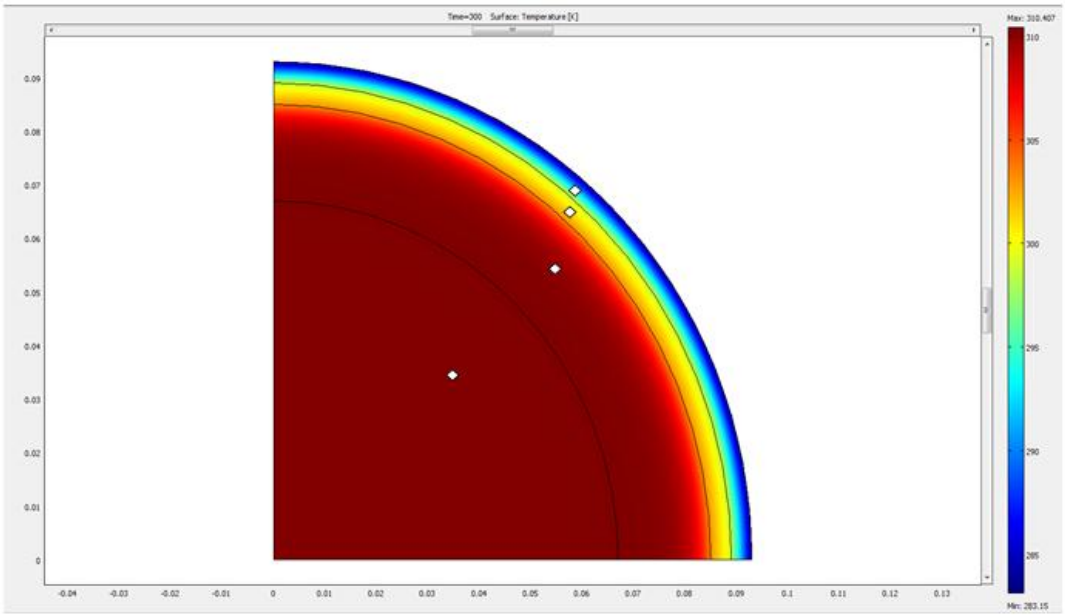


Figure 10: Temperature profile of the adult brain model after six hours. The white marks indicate points used in the sensitivity analysis of each layer.

Like the infant model, the adult model shows that steady state was reached relatively quickly due to the fact that the blood temperature remains constant over time and the volumetric flux of blood in the gray matter is large (Figure 11). However, unlike the infant model, the adult model shows less cooling of the gray matter. Also, compared to the infant model, the bone layer in the adult head cools more gradually. This is again due to the higher blood perfusion rates in all the layers, as the blood in the larger capillary network delivers heat from the body core to the brain, slowing down the cooling process.

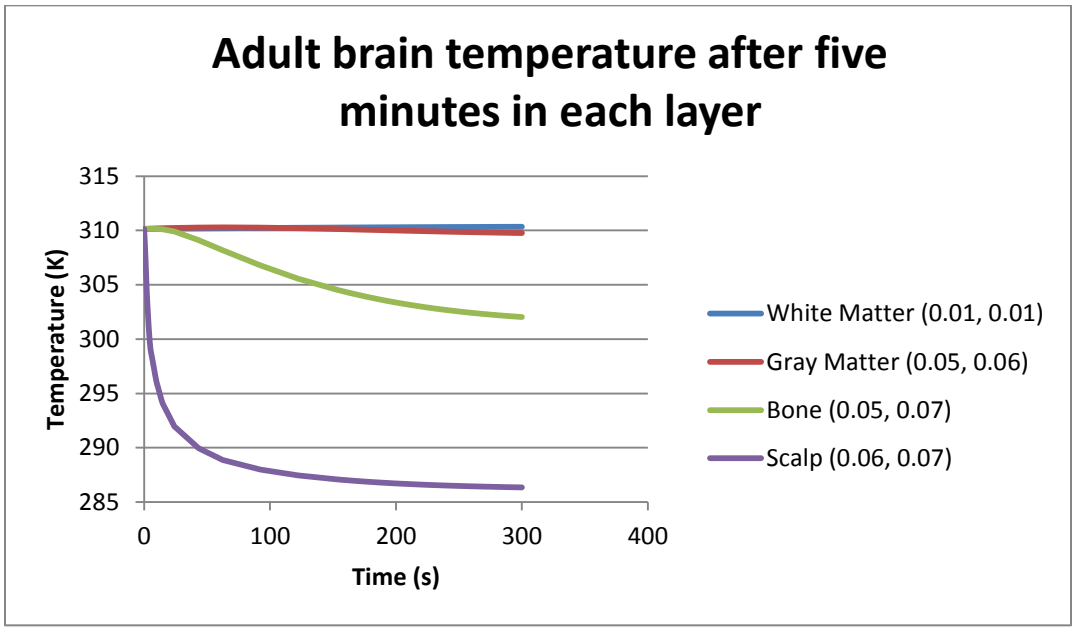


Figure 11: Plot of adult brain temperature in each subdomain of model after five minutes. Steady state temperatures are approached quickly.

We performed an analysis similar to the infant model, of temperature by radius of the head, to quantify the difference between the adult and infant models. We assumed that the same 3°C threshold as was used for the infant was appropriate for the adult model. As shown in Figure 12, cooling below 34°C was largely limited to the bone and scalp regions of the adult head. We calculated that approximately 17% by volume of the gray matter cooled below the desired threshold in the adult model. Assuming that the mechanism of hypoxia is comparable in infants and adults, we conclude that the 17% cooling of the gray matter is not sufficient to be therapeutic, compared to the 51% gray matter cooling in infants. Therefore, the model is inconclusive about the potential benefits of using hypothermia to treat hypoxia in adults.

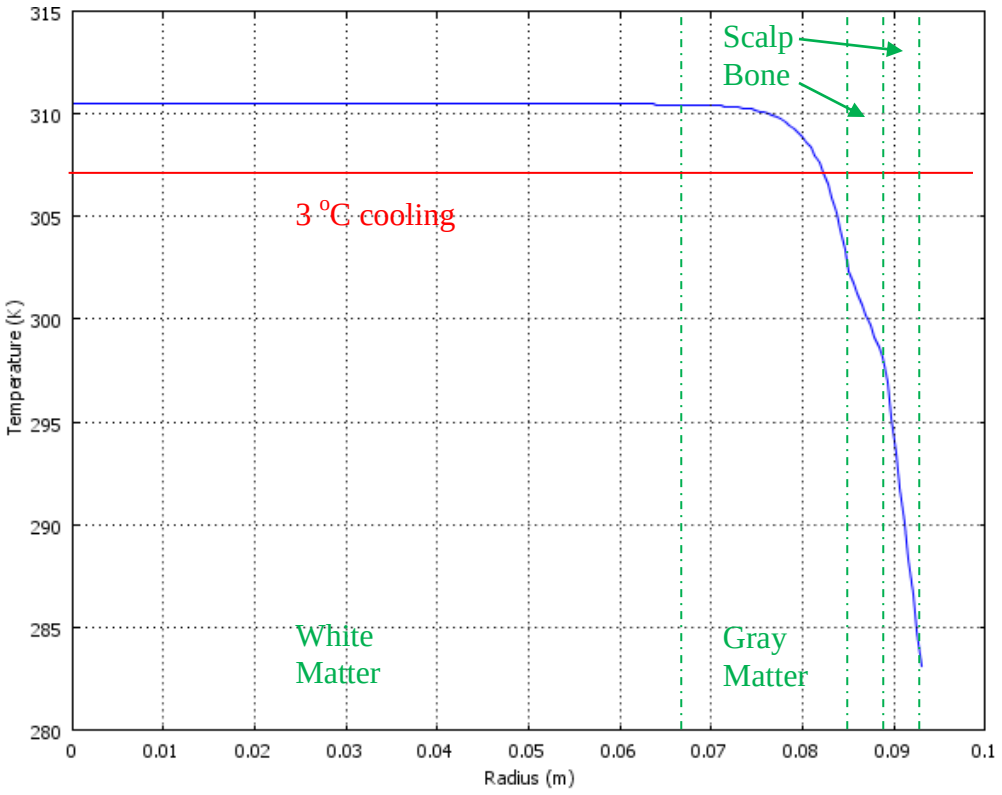


Figure 12: Steady-state temperature profile of the adult brain, viewed after six hours of application. Cooling is limited to the scalp and bone regions of the brain, with little cooling penetrating into the gray matter. As for the infant, no cooling is observed in the white matter.

5c. Discussion

i. Accuracy Check: Comparison of Model Results with Literature

To confirm that our model represents the actual heat transfer processes occurring in the brain during selective head cooling, previously published models found in literature are used as a comparison. The models of brain cooling by Diao and Niemark were used in the accuracy check[5, 21]. While each model uses slightly different methods and parameters, results should be comparable if our model is accurate. We note that literature models were scaled accordingly to be comparable by radius to our model.

Figure 13 shows the temperature profile of the adult brain obtained through the three different models for brain cooling. A similar decline in temperature is observed in all the models. Although the models do not yield identical temperature profiles, the general trend in temperature is very similar between our model and those created by Niemark and Diao. The variations can be attributed to different models taking measurements at different time periods. For example, while our model and the model by Niemark measured brain temperature after six hours, the Diao

model measured temperature at steady state. In addition, there were different assumptions used in defining the geometry and different parameter values used which would contribute to the variability seen in the temperature profile.

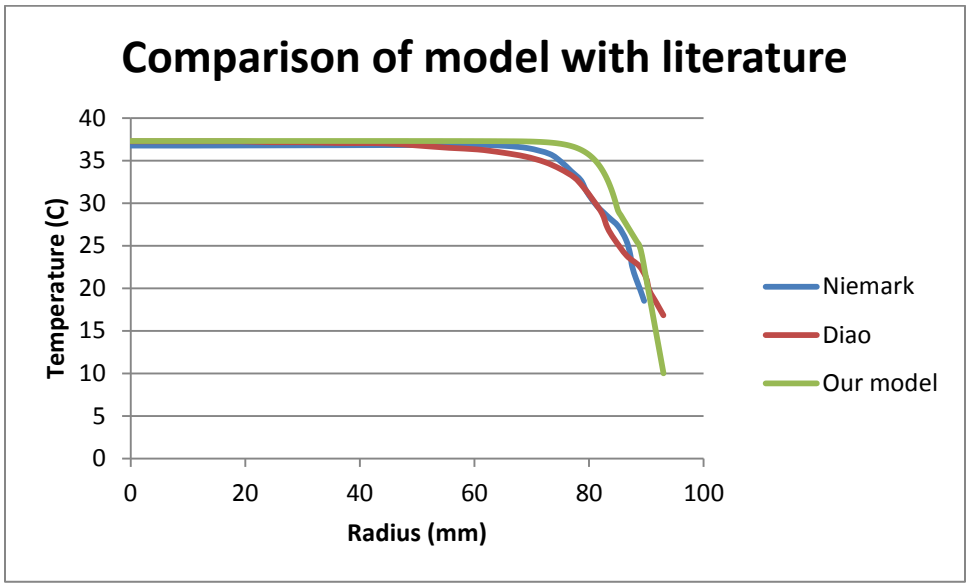


Figure 13: Comparison of selective brain cooling model with those found in literature.

ii. Sensitivity analysis

Considering that parameters found in literature are dependent on the source and methods of determination, there is often variability in reported parameter values. A sensitivity analysis was completed to see the effect of this variability on the results of the adult model. Deviations were applied for some parameters to see the responsiveness of the model to these changes. The parameters under consideration were metabolic heat, thermal conductivity, density, and blood perfusion rate. These parameters were changed within the gray matter layer of the adult model, as the cooling of this layer is most important for therapy. For each parameter, the steady state temperature, taken after 6 hours, within each layer was modeled. The points used to represent each layer were 0.035 and 0.035 for white matter, 0.055 and 0.055 for gray matter, 0.058 and 0.065 for the bone layer, and 0.059 and 0.069 for the scalp (Figure 9). Figure 14 shows that varying these parameters by 5-10% in the gray matter had a negligible effect on the steady state temperature of the adult model. The results of our sensitivity analysis show that temperature change is relatively insensitive to changes in the physical parameters of the head.

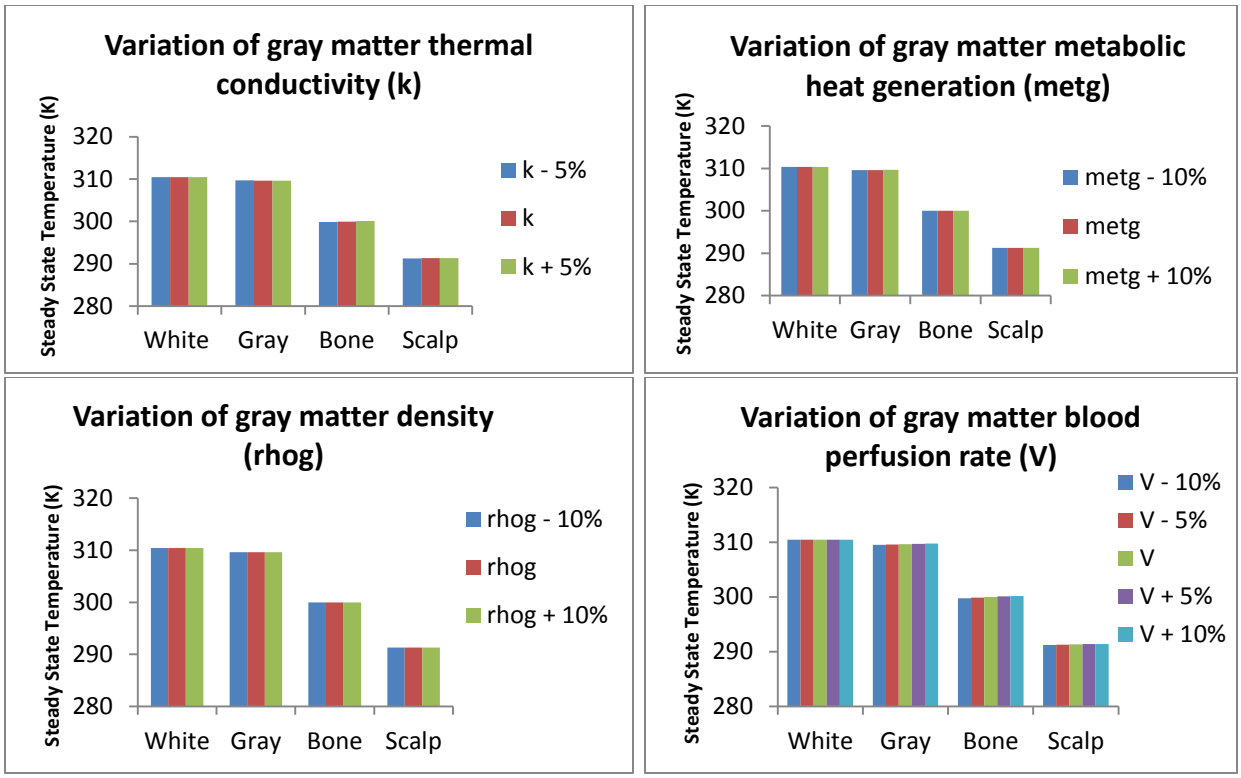


Figure 14: Sensitivity analysis varied metabolic heat, conductivity, density, and perfusion rate within the gray matter layer and measured the resulting change in each layer of the model. The plots show temperature differences in each layer of the adult brain by varying each parameter independently. A 10% change in either direction of any of these four parameters did not change the steady state temperature of each layer.

As the next step, we hypothesized that lowering the cap temperature in the adult model may elicit cooling deeper into the brain, thus potentially making the cool cap a plausible treatment for adults. To investigate this hypothesis, a change in the temperature of the cap was modeled. The adult model was considered with the cap temperature when implemented as a constant temperature boundary condition and varying from 0-14°C. Over this range, the steady state temperature in the scalp and bone changed, but the white and gray matter temperature change was very small (Figure 15). Comparing the sensitivity analysis for all the factors considered, the most responsive was cap temperature, as there was a maximum change of 0.407°C in the gray matter when the cap temperatures were varied from 0 to 14°C. Still, this change does not have a substantial effect on the brain temperature and can be considered to be relatively insignificant.

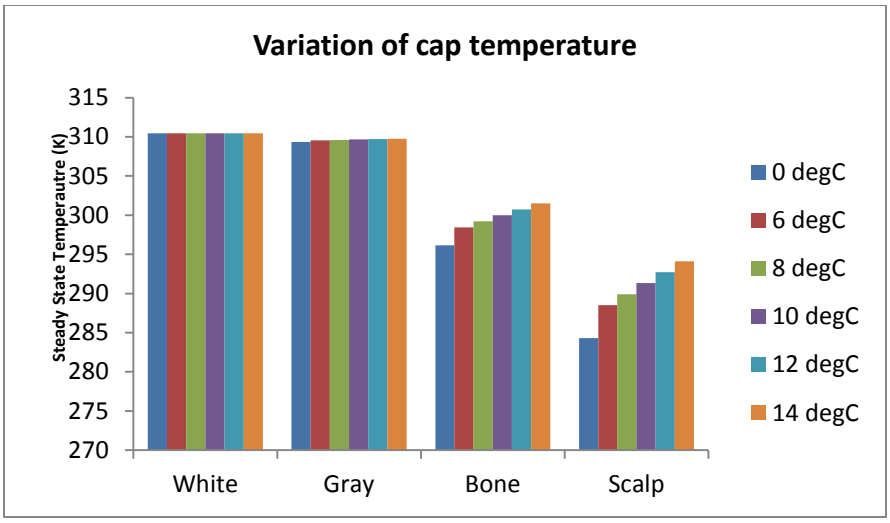


Figure 15: Variation of cap temperature in the adult model changed the steady state temperature of the bone and scalp layers, but not the gray or white matter layers, where lower temperature is preferred. Thus cooling the cap further would not offer greater efficacy for adult patients.

iv. Design Goals

We see that the CoolCap is unlikely to work for an adult within the relatively broad range of tested parameters, assuming that hypoxia in infants and adults require the same amount of cooling in the gray matter. No parameter variation increases cooling deeper into the brain (above the initially observed 17% by volume) for the adult model. Even with decreased blood perfusion or a colder cap temperature, cooling fails to significantly penetrate into the gray matter. This implies that the parameter dictating whether surface cooling will be effective is likely the size of the head. In the infant model, therapeutic cooling was possible with a 10°C cap. However, in the adult model, similar cooling was not possible over a range of parameter conditions. In the context of design, these results suggest that surface cannot be confirmed as a viable brain cooling method after infanthood due to the increase in head size.

6. Conclusions

This study was based on a parallel drawn between neonate victims of HIE in danger of severe brain damage and at-risk patients of stroke and heart attack. In both cases, the danger of brain damage is high and an immediate and timely solution is necessary to prevent severe disability or death of patients. The strategy employed here was to develop a model of existing proposed therapies of HIE in infants, validate it, and use it as a basis for a similar model of adults. The first goal of this study was to validate the cooling cap system through a model of the cap as a constant heat sink applied to an infant's head. In addition to giving insight into the mechanism of hypothermia to prevent brain damage, the infant model would be a validated

comparison against the adult model. Based on these initial results, we hoped to test whether a similar approach can be applied to adults, as has been suggested by multiple studies. [1,4,7,9,11,13]

In the infant model, we observed that the temperature dropped by 3°C halfway into the gray matter of the brain (51% by volume). According to multiple animal studies and clinical trials this is the suggested temperature drop to ensure that brain damage is prevented or at least greatly reduced. [2,6,12,14] Our study therefore serves as a mathematical validation to numerous experimental studies done in this field. What is unique about our work is that our findings suggest that cooling of the entire brain is not necessary to prevent brain damage. Experiments have proven that hypothermia is effective for treating HIE. As a model for this process, our work gives insight into the mechanism of *how* this is achieved, on a macro scale. These findings may shed light upon the chemistry of HIE and its effect on the brain. We note, however, that the white and gray regions are not as well defined in a real human brain, so some caution must be taken in interpreting these results. Nevertheless, though the exact numerical values and geometries may vary from patient to patient, this study clearly suggests that it is not necessary to cool the whole brain to prevent brain damage, thus implying that the damage may be occurring mostly in the outer gray matter of the brain. These results may be of use to researchers studying the effect and cause of HIE in neonates.

With these assumptions, we proceed to attempt a similar solution for an adult head geometry, as a model for stroke and cardiac arrest patients in danger of severe neural degradation. The size of the head is increased accordingly. Additionally, blood perfusion rates in the layers of the adult head are increased between 4 and 7 times as compared to rates in infants, depending on the head region. The results show, however, that the drop in temperature is not as significant in the gray matter in the steady state. Compared to 51% cooled gray matter by volume in the infant, only 17% of the gray matter is cooled in the adult. This leads us to conclude that in fact a cooling cap would be ineffective for treating stroke and cardiac arrest patients. Even if the partial cooling in the adult has positive effects, this study is inconclusive to recommend such treatment without further research. To understand this result, we tested the sensitivity of our model to various material properties, hypothesizing that our solution was potentially invalid if a particular material value had a great effect on the solution and was wrongly chosen. Our sensitivity analysis, varying the effect of varying metabolic heat, conductivity, density, and perfusion rate, showed that none of the properties had a large enough effect on the solution to invalidate our conclusions. We were particularly interested in seeing the result of varying blood perfusion rate, as this was the most significant change between infant and adult models. We did not find that up to 10% variation in either direction had an effect on the temperature of the brain.

Finally, we wanted to test whether by varying the cap temperature we could induce cooling deeper into the brain. This was a viable hypothesis as a lower cap temperature could increase heat flux out of the inner regions of the brain. We found that this was not the case, as the temperature dropped significantly only in the bone and scalp regions of the head. Based on this analysis, we conclude that the larger size of the adult head prevents therapeutic cooling from penetrating deeper into the gray matter. Therefore, contrary to studies claiming that cooling therapy could be effective in treating stroke and cardiac arrest patients, we would *not* recommend such therapy based on our results. We propose as further research the possibility of combining a drug therapy[15] with the head cooling therapy, or a cooling catheter, as surface

cooling alone has shown to be effective only when the size of the head and the blood perfusion rates are low as in infants.

6a. Economic Impact and Future Research

The high number of people who require HIE treatment creates a large potential market for pharmaceutical companies. Therefore our results have crucial implications on the industry. The ineffectiveness of cooling therapy treatment in adults helps companies avoid expensive, large-scale studies which are not supported by theory, visible through our model. While a positive result would have been optimal, the negative result inhibits companies from losing money and potentially saves people's health from inadequate treatment.

While CoolCap brain cooling is not an effective method of treating stroke and cardiac arrest in adults, the concept of lowering brain temperature to prevent brain damage still holds true. Therefore an alternate method of lowering brain temperature should still be an effective treatment for adult patients. Possibilities of such include inserting cooling pads surgically or decreasing the entire body temperature to lower the heat gain due to perfusion. These theoretical concepts provide a bright future for patients, but require additional extensive research.

7. Appendix A: Mathematical Statement of Problem

7a. Governing Equations

To model the temperature profile of the head and brain over time during surface cooling, the heat transfer equation for a 2D-axisymmetric model was solved. Included were transient, conduction, perfusion, and heat generation terms. Convection was not modeled as blood flow was incorporated in the perfusion term. The initial condition used was that the entire head started at 37°C.

$$\rho C_p \frac{\delta T}{\delta t} = k \frac{1}{r^2} \frac{\delta}{\delta r}\left(r^2 \frac{\delta T}{\delta r}\right) + \frac{\rho c \dot{V}(T_a - T)}{Vol} + Q \qquad (4)$$

In equation 4, ρ is the density of each layer, C_p is the heat capacity of each layer, k is the conductivity of each layer, and Q is the metabolic heat generation in each layer (constant). Within the perfusion term, ρ is the blood density, c is the blood heat capacity, $\dot{V}$ is the perfusion rate, T_a is the arterial blood temperature (constant 37 °C), and Vol is the volume of each layer. The independent variables are time (t) and radius (r), and the dependent variable is temperature (T).

The boundary conditions implemented are listed below:

--Thermally insulated along the horizontal axis (head/neck boundary)
--Axisymmetric about the vertical axis
--Constant temperature along the head surface
--Continuity between each layer

7b. Model Parameters

Layer	Constant	Infant Value	Adult Value	Units
Scalp	Density	1000	1000	kg/m^3
	Conductivity	0.34	0.34	W/m K
	Heat Capacity	4000	4000	J/kg K
	Perfusion Rate	1.316E-08	6.940E-08	m^3/s
	Volume	3.941E-05	2.082E-04	m^3
	Metabolic Heat Generation	363.4	363.4	W/m^3
	Thickness	0.002	0.004	m
Bone	Density	1500	1500	kg/m^3
	Conductivity	1.16	1.16	W/m K
	Heat Capacity	2300	2300	J/kg K
	Perfusion Rate	1.650E-08	8.564E-08	m^3/s
	Volume	3.665E-05	1.903E-04	m^3
	Metabolic Heat	368.3	368.3	W/m^3

	Generation			
	Thickness	0.002	0.004	m
Gray Matter	Density	1050	1050	kg/m^3
	Conductivity	0.5	0.5	W/m K
	Heat Capacity	3700	3700	J/kg K
	Perfusion Rate	2.192E-06	9.188E-06	m^3/s
	Volume	1.566E-04	6.563E-03	m^3
	Metabolic Heat Generation	16700	16700	W/m^3
	Thickness	0.011	0.018	m
White Matter	Density	1050	1050	kg/m^3
	Conductivity	0.5	0.5	W/m K
	Heat Capacity	3700	3700	J/kg K
	Perfusion Rate	1.086E-06	4.410E-06	m^3/s
	Volume	3.103E-04	1.260E-03	m^3
	Metabolic Heat Generation	4175	4175	W/m^3
	Thickness	0.042	0.067	m
Blood	Density	1050	1050	kg/m^3
	Heat Capacity	3800	3800	J/kg K

Table 1: Material properties and input parameters for our model.[3,5,8]

7c. Solution Strategy

We used the COMSOL Multiphysics transient heat conduction solver to arrive at a solution based on the parameters. The brain was assumed to be a hemisphere and was therefore modeled in a two dimensional axisymmetric plane, with symmetry along the y-axis. This allowed for fewer computations with similar results found in a three dimensional model. The bottom of the brain (x-axis) was assumed to have zero flux and the outer skin boundary was assumed to be in close contact with a constantly cold CoolCap, producing a 10°C boundary. The steady state model was run for 6 hours (21,600 seconds) with a time step of 60 seconds.

8. Appendix B: Analytical solution strategy

Given an axisymmetric hemisphere of radius 6 cm, equation (1) can be solved by assuming a hyperbolic profile using the boundary conditions T(r=0) = 37°C and T(r=R) = 10°C.

$$\left(\frac{\mathrm{k}}{\mathrm{r}^2}\right) \times \left(\frac{\mathrm{d}}{\mathrm{dr}}\right)\left[r^2 \times \frac{dT}{dr}\right] = 0 \qquad (5)$$

Simplify using product rule for d/dr term:

$$\frac{d^2T}{dt^2} = -\frac{2}{r} \times \frac{dT}{dr} \qquad (6)$$

From here we assume the solution will have form dT/dr = A/r, where A is a constant, yielding equation (7).

$$\frac{dT}{dr} = -\frac{A}{r^2} \qquad (7)$$

Solving equation (7):

$$T = -\frac{A}{r} + B \qquad (8)$$

In equation (8) B is also a constant. Now use boundary conditions that T(r=0) = 37 °C and T(r=R) = 10 °C. Since A/0 = -inf, we estimate zero as 0.1, assuming 0.1 << R. Then A and B can be solved for:

A = -0.24
B = 9.98

Then we can plot T versus r with R = 6 cm using the equation T = -2.7458/r + 9.542 over the domain 0.1 < r < 6. This plot is shown in Figure 3.

9. Appendix C: References

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