



Clinical Study

# Simple intravenous fluid regimens to control fever in hospitalized stroke patients: A theoretical evaluation

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Received 3 October 2007; accepted 2 April 2008

## Abstract

Fever is an independent predictor of worse outcome in stroke patients. We hypothesized that a peripheral infusion of saline in chilled or ice slurry form can be a practical adjuvant therapy to maintain euthermy. We developed a theoretical model simulating systemic body cooling in response to 0 °C saline and 50% ice slurry. Temperature elevations up to 39 °C were studied with respect to the time needed to reach a core temperature of 37 °C. Mathematical modeling identified a cooling rate of 0.48 °C/hr and 0.24 °C/hr using a 450 mL/hr infusion of 50% ice slurry and chilled saline. A reduction of the infusion rate to 150 mL/hr decreased euthermy time by a factor of 3; however, the total amount of coolant remained constant. Thus, based on mathematical modeling, peripheral infusions of saline in chilled or ice slurry form can be used as an adjunct therapy to achieve euthermy and control fever. Using intravenous coolants in an on-demand, temperature-guided and supervised treatment setting seems most reasonable to avoid potentially unsafe use of extended fluid volumes and infusion times.

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**Keywords:** Brain cooling; Euthermy; Intravenous cooling; Modeling

## 1. Introduction

Stroke patients exhibit elevated body temperature during acute and subacute recovery phases. Castillo et al. reported that 60% of 260 patients with acute hemispheric infarction developed hyperthermia (axillary temperature >37.5 °C) within 72 hours of hospital admission. The three-month mortality rate in this patient subset was significantly higher than those who remained normothermic (1% vs. 15.8%, respectively,  $p < 0.001$ ).<sup>1</sup> Reith et al.<sup>2</sup> 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,<sup>3–8</sup> but not all,<sup>9</sup> have corroborated these findings; hence, maintaining euthermy body temperature (near 37 °C) throughout hospitalization appears to be a logical step towards improvement of outcome. Therefore, a simple and effective method to maintain euthermy in stroke patients throughout the initial injury and recovery periods may be of significant benefit, especially given the magnitude of non-critically ill patients with acute cerebrovascular injury.

Current fever reduction strategies are either relatively safe but only modestly effective (including antipyretics,<sup>10,11</sup> blankets, or garments<sup>12</sup>), or more effective, but invasive and elaborate, such as endovascular cooling or extracorporeal heat exchange.<sup>13,14</sup> Limitations in procedural accessibility and nursing care availability further prohibit more complicated methods to reduce fever, highlighting the need for a safe, simple and cost-effective cooling strategy for

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stroke patients, particularly those non-critically ill admitted to the regular ward.<sup>15–17</sup>

Based on clinical observations and theoretical cooling analyses,<sup>18–20</sup> we were interested in whether intravenous (IV) infusions of chilled crystalloid or designer ice slurry/saline solutions, adjusted for safety and efficiency to daily fluid requirements and temperature fluctuations, would conveniently and inexpensively control fever. Intravenous fluids are routinely administered to patients with cerebrovascular events to stabilize intravascular volume and improve systemic cardiovascular function and brain perfusion.<sup>21,22</sup> To induce hypothermia among comatose survivors of out-of-hospital cardiac arrest, two pilot studies found peripheral infusions of ice-cold (4 °C) ringer solution safe.<sup>23,24</sup> In addition, when studying novel designer cooling fluids, Vanden Hoek et al. used ice slurry mixed with normal saline (1:1) in the porcine model, and found that target core temperature could be reduced to <34 °C twice faster than with saline alone.<sup>25</sup>

Our objective was to theoretically evaluate the potential for cooled peripheral IV infusions to maintain eutermic or near-eutermic temperatures in cerebrovascular victims. We evaluated the use of: (i) a microparticulate slurry (MPS) coolant – a two-phase fluid composed of smooth, highly flowable globular ice particles of <100 µm in diameter suspended in normal saline, and (ii) cooled saline solution.<sup>25</sup> We based our analysis on fluid infusion rate, duration, volume, and simulate reductions in core temperatures through infusions at different cooling temperatures, using two different coolant types. Our main outcome parameters were the infusion amount and time required to achieve eutermia in a hypothetical febrile patient.

## 2. Materials and methods

We simulated cooling human blood by analyzing both the thermal interaction between warm blood and cold solution during IV infusion and the resulting temperature distribution within the human body, which was modeled as a cylinder (Supplementary Fig. 1). Conceptually, the change of arterial blood temperature is induced by two steps: (i) mixing of warm blood and cold IV fluid; and (ii) thermal interactions between the blood and the human body. Since the organ temperature is higher than the blood temperature, heat transfer is directed from the organs to the circulating blood, with the blood temperature being reduced by a continuous infusion of cooled IV fluids. Accordingly, we first analyzed the expected reductions in blood temperature during infusion of cooled fluids and then used the Pennes bioheat equation to estimate the rate of heat transfer between body mass and blood during the temperature distribution throughout the body. The two steps combined would estimate realistically how an IV infusion coolant changes core body temperature. The physiological parameters and thermal properties used in all simulations are shown in Table 1. The initial blood temperature,  $T_{b0}$ , was assumed to be 39 °C. The IV infu-

Table 1  
Thermal properties of ice (water), saline, and blood, including density, specific heat and latent heat

	Density $\rho$ (kg/m <sup>3</sup> )	Specific heat $c$ (J/kg °C) <sup>a</sup>	Latent heat of ice (J/kg) <sup>b</sup>
Ice (water)	1000	4180	$333.5 \times 10^3$
Saline	1000	4180	
Blood	1050	3700	

<sup>a</sup> Specific heat = energy (Joules) needed to increase the temperature of 1 kg mass by one degree Celsius (J/kg °C).

<sup>b</sup> Latent heat = total energy required for 1 kg ice at 0 °C to change to its liquid phase (water) at the same temperature (J/kg).

sion rate ranged from 150 mL/hr to 450 mL/hr and was varied in the model according to the core temperature changes. Two coolant types were considered: saline at 0 °C and saline at 0 °C with a 50% ice slurry.

### 2.1. Thermal interactions between blood and body mass

For simplicity, the human body was modeled as a cylinder of 0.24 m in diameter and 1.6 m in height equivalent to a total body weight of 70 kg (Supplementary Fig. 1). In our theoretical analyses, the body was exposed to thermal convection and radiation environmental influences via the skin surface. The body's metabolism, or heat generation, was modeled as a heat source within the cylinder. Blood perfusion was modeled as either a heat source when the arterial temperature was higher than the local tissue temperature, or a sink when the temperature was lower. The governing equation for the temperature field in tissue can be written (Eq. (1)) as:

$$\rho c \frac{\partial T_t}{\partial t} = k_t \nabla^2 T_t + q_m + \rho c \omega (T_a - T_t) \quad (1)$$

where  $\rho$  is density,  $c$  specific heat,  $k_t$  thermal conductivity of tissue,  $q_m$  volumetric heat generation rate (W/m<sup>3</sup>), and  $\omega$  local blood perfusion rate. In Eq. (1) blood perfusion acts as a heat source if local temperature is higher than the blood temperature; however, one expects that heat is transferred from tissue to blood if the blood temperature is lower. The Pennes bioheat equation simplifies the vasculature by modeling blood flow as a source term. This equation has been used extensively to model tissue temperature field for various clinical applications and is considered an accurate description of tissue temperature field.

Based on our previous theoretical modeling, the maximum temperature of the body was assumed to be located in the center of the cylinder with tissue temperatures decreasing toward the skin/cylinder surface. From determination of the blood temperature  $T_a$  the average body temperature  $\bar{T}_t$  was predicted by solving for Eq. (1). We emphasize that in Eq. (1), the arterial temperature  $T_a$  was used as an input. To predict the body temperature response to a change in the arterial blood temperature, the thermal interaction between blood and tissue needs to be determined. Therefore, we developed a mathematical equation

to determine the blood temperature as a function of time (Section 2.2).

### 2.2. Energy balance in blood

Because of the relatively short recirculation time, blood in the human body was considered as a single compartment. We assumed a total blood volume of the body,  $V_{blood}$ , to be 5 L. A mathematical expression of the energy absorbed or removed per unit time was determined by the temperature change of the blood, as follows:

$$\rho_{blood}c_{blood}V_{blood}[T_a(t + \Delta t) - T_a(t)] \quad (2)$$

where  $T_b(t)$  was blood temperature at time,  $t$ , and  $T_b(t + \Delta t)$  at time  $t + \Delta t$ ;  $\rho_{blood}$  the blood density ( $\text{kg/m}^3$ ), and  $c_{blood}$  ( $\text{J/kg } ^\circ\text{C}$ ) the specific heat of blood that measures the energy (J) needed to raise or decrease the temperature of 1 kg blood by  $1^\circ\text{C}$ . In the model, the IV coolant removed energy from the blood, inducing heat loss from the body tissue. Therefore, the governing equation for the blood temperature was written as follows:

$$\rho_{blood}c_{blood}V_{blood}[T_a(t + \Delta t) - T_a(t)] = [Q_i(T_a) - Q_{blood-tissue}(t)]\Delta t \quad (3)$$

where  $Q_i$  was the heat removed by the coolant per second, and  $Q_{blood-tissue}$  the heat transfer to the body tissue per second. The  $Q_{blood-tissue}$  was determined by integrating the perfusion source term in Eq. (1); that is:

$$Q_{blood-tissue}(t) = \int_{body} \int_{volume} \rho c \omega (T_a(t) - T_i(r, t)) dV_{body} \approx \rho c \bar{\omega} (T_a(t) - \bar{T}_i(t)) V_{body} \quad (4)$$

where  $\bar{T}_i$  was the average body tissue temperature as determined by solving the Pennes bioheat equation,  $\bar{\omega}$  the average blood perfusion rate, and  $V_{body}$  is the total blood volume.

To derive  $Q_i$ , we analyzed the thermal interactions between the blood and coolant during IV infusion with the coolant flow rate being  $P_i$  (mL/hr). We defined further that the IV solution consists of  $d\%$  by volume of saline and  $(100-d)\%$  of ice slurry at a temperature of  $0^\circ\text{C}$ . If the IV solution was pure saline,  $d$  was equal to 100.  $Q_i$  was given by:

$$Q_i = \rho_{saline}c_{saline}P_i(d\%)\Delta t[T_{saline} - T_b(t)] + \rho_{water}c_{water}P_i[(100-d)\%]\Delta t[T_{saline} - T_b(t)] - \rho_{water}P_i\Delta t[(100-d)\%]h_{fg} \quad (5)$$

where  $P_i$  was the flow rate of the IV solution (mL/hr),  $T_{saline}$  the temperature of the IV solution at entry point, and  $h_{fg}$  the latent heat (J/kg) that accounts for the energy needed during the phase change from ice to water. The first two terms on the right-hand side of Eq. (5) identify the energy removed by raising the temperature of the saline and water from  $T_{saline}$  to  $T_b$ , and the third term the energy

needed for the phase change from ice to water at  $0^\circ\text{C}$ . To solve Eq. (3) and to determine  $\bar{T}_i$ , both Eqs. (1) and (3) were solved simultaneously.

### 3. Results

Supplementary Fig. 2 provides a schematic view of the typical temperature distribution between body core and outer surface. We considered an average blood perfusion rate of 7 mL/min 100 g tissue as determined by stroke volume of 70 mL and the heart rate of 75 beats/min. This results in a metabolic heat generation of  $1428 \text{ W/m}^3$  using an average of 2000 kCal/day of food consumed. With the initial blood temperature selected as  $39^\circ\text{C}$  the resultant temperature gradient had a maximum temperature at the innermost center of  $39.3^\circ\text{C}$  and an outer surface temperature of  $35.1^\circ\text{C}$ .

Supplementary Fig. 3 illustrates the time-dependency of the core blood temperature for the two coolants under consideration. As expected, during IV infusions of the coolant the blood temperature remained slightly but consistently lower than the expected organ temperature. Assuming a constant peripheral infusion rate of 450 mL/hr >4 hours are required to lower the core temperature to  $37^\circ\text{C}$  using 50% ice slurry as a coolant. The time would almost double if  $0^\circ\text{C}$  saline were used.

Supplementary Fig. 4 depicts the hourly cooling rate for both coolants at an infusion rate of 450 mL/hr. For slurry coolant, the initial blood cooling rate is higher than the body cooling rate due to infusion of ice microparticles directly into the blood; however, the cooling rates stabilize for both blood and body temperature after about 10 min. Infusions of  $0^\circ\text{C}$  saline or 50% ice slurry infusion achieved approximate cooling rates of  $0.24^\circ\text{C/hr}$  and  $0.48^\circ\text{C/hr}$ , respectively. Thus, based on the infusion rate of 450 mL/hr about 1.88 L of IV slurry and 3.75 L of  $0^\circ\text{C}$  saline are needed to achieve eutheria in a patient with a core temperature of  $39^\circ\text{C}$ .

Supplementary Fig. 5 illustrates the estimated cooling rate ( $^\circ\text{C/hr}$ ) for slurry dependent on the peripheral infusion rate. Decreasing the infusion rate from 450 mL/hr to 150 mL/hr essentially reduces the cooling rate by a factor of three. However, the total amount of required infusion fluid ( $\sim 2$  L) remained largely independent of the infusion rate. This seems realistic since the body temperature reduction is determined by the total amount of heat removed, of which the total infusion volume is an estimate.

### 4. Discussion

We aimed to find a safe, simple, and inexpensive method to achieve and sustain eutheric temperatures in acute, non-critically ill stroke patients. We used mathematical modeling to evaluate the usefulness of peripheral infusions of coolants such as  $0^\circ\text{C}$  saline and 50% ice slurry to maintain eutheria.<sup>25</sup> Our results indicate that the core temperature of a patient with a fever of  $39^\circ\text{C}$  can be lowered to

37 °C in about 4 hours with an infusion rate of 450 mL/hr with a 50% ice slurry. However, using 0 °C saline, which has significantly less cooling capacity compared to ice slurry, would double the time required to achieve eutheria. Or stated differently, at an infusion rate of 450 mL/hr the expected reduction in core temperature is 0.48 °C/hr and 0.24 °C/hour for ice slurry and 0 °C saline, respectively. This translates to a total peripheral infusion volume of about 3.75 L of 0 °C saline to decrease the body temperature by 2 °C. The volume of infused cooled saline for a 2 °C core temperature drop is rather constant and relatively independent of the infusion rate (this is, reducing the infusion rate from 450 mL/hr to 150 mL/hr would triple the required time to achieve eutheria as the amount of total coolant needed remains approximately the same).

Normal saline is the preferred resuscitation fluid for patients with neurological and neurosurgical injuries. It is also cheap, easy to store, and very frequently utilized as hydration fluid in hospitalized patients. Ice slurry, in contrast, is a designer coolant and resuscitation fluid of increasing clinical interest. It has proven efficacy in animal testing,<sup>25</sup> a stronger cooling capacity per unit volume, and, compared with 0 °C saline, 50% ice slurry–saline mixtures roughly halve hourly cooling rates and volume. The use of cooled peripheral infusions is safe and is probably without significant side effects. Active maintenance of eutheria (36.5–37.3 °C) in awake stroke patients using cooled intravenous fluids seems unlikely to induce discomfort or significant side effects. Lopez et al.<sup>26</sup> infused 4–6 L of 3 °C lactate ringer at ~0.1 mL/kg per minute into healthy, awake volunteers to demonstrate the lack of side effects. Shivering, which was observed in control patients between 35.6 °C and 36.8 °C, was avoided as skin temperature was maintained above 36.7 °C.<sup>26</sup> Infusing healthy, awake volunteers with 4 °C intravenous fluids at 40 mL/kg per hour, Frank et al.<sup>27</sup> demonstrated that the first signs of thermal discomfort occurred only when the body temperature reached 36 °C. Because of a lower shivering threshold, the elderly may be more susceptible to infusions of coolants compared to the younger population;<sup>28</sup> however, no cardiac abnormalities were observed in the same group during or after the cold fluid infusions.<sup>29</sup>

Our results indicate that peripheral infusions of normal saline or ice slurry at <500 mL/hr are potentially useful to help maintain eutheria in febrile, non-critically ill patients, and that these can be viewed as a supplement to already established pharmacological and surface cooling approaches. The attractiveness of this approach is because cooling saline prior to infusion is simple and safe (for example, used in a volume-controlled, temperature-adjusted, peripheral infusion regimen to maintain eutheria in a stroke patient with fluctuating subfebrile temperatures during the first days of admission). Our study provides the theoretical basis for a flexible peripheral infusion schedule of a coolant with use of higher infusion rates temporarily during febrile episodes and subsequent rate reduction of the infusion once eutheria is achieved. In our experience, most

stroke patients without signs of infections do not experience many febrile episodes; however, exact data on fever frequency are not available. Assuming that even small temperature reductions may improve overall outcome in stroke patients, a peripheral infusion of a coolant (rate-adjusted to the body temperature) would be a simple, practical, and suitable approach for most ischemic stroke patients while being a non-invasive, universally applicable, and cost-effective technique, requiring minimal additional nursing care.

Our theoretical model has inherent limitations.<sup>30</sup> We reduced the human body in our model to a simple cylinder, which does not accurately predict the detailed temperature variation within the body. However, it seems appropriate to simulate instead the average body temperature because it considers the overall thermal balance among body tissue, blood, and the surrounding environment. Furthermore, the mathematical model we used is based on well-established bioheat transfer analyses, including well-specified physiological parameters and thermal properties. Similar models have been experimentally verified.<sup>18–20</sup>

Other factors not taken into account in our model may modify the obtained simulation results. Cooling rate, for example, will increase by 40% if body mass is 50 kg (0.67 vs. 0.48 °C/hr). Temperature elevation of patients with extreme body mass indices may not respond predictively to IV infusions of coolants. Our mathematical simulation also assumes that no change of thermal regulation occurs during cooling. If during cooling, the body redistributes blood perfusion from an internal organ, and/or sweating occurs at the skin surface, the cooling rate would be higher than that predicted by the current model.

### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jocn.2008.04.003.

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