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10.4103/bc.bc\_48\_19

# Infusion warm during selective hypothermia in acute ischemic stroke

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## Abstract:

**INTRODUCTION:** Mechanical thrombectomy (MT) has dramatically improved the prognosis for acute ischemic stroke (AIS) patients. Despite high recanalization rates, up to half of the patients will not present a good neurological outcome after MT. Therapeutic hypothermia is perhaps the most robust neuroprotectant studied preclinically.

**MATERIALS AND METHODS:** We explored various warming effects that can reduce the effectiveness or potency of selective hypothermia during AIS under conditions similar to actual clinical care. Four different selective hypothermia layouts were chosen. Layouts 1 and 2 used a single catheter without and with an insulated IV bag. Layouts 3 and 4 used two catheters arranged coaxially, without and with an insulated IV bag. Independent variables measured were IV bag exit temperature, catheter inlet temperature, and catheter outlet temperature at four different flow rates ranging from 8 to 25 ml/min over an infusion duration of 20 min.

**RESULTS:** Dominant warming occurs along the catheter pathway compared to warming along the infusion line pathway, ranging from 66% to 72%. Coaxial configurations provided an approximate 4°C cooler temperature benefit on delivered infusate over a single catheter. Brain tissue temperature predictions show that the maximum cooling layout, Layout 4 at maximum flow provides a 1°C within 5 min.

**CONCLUSION:** Significant rewarming effects occur along the infusate flow path from IV bag to site of injury in the brain. Previous selective hypothermia clinical work, using flow rates and equipment at conditions similar to our study, likely produced rapid but not deep tissue cooling in the brain (~ 1°C).

## Keywords:

Acute ischemic stroke, mechanical thrombectomy, selective hypothermia

## Introduction

Mechanical thrombectomy (MT) has dramatically improved the prognosis for acute ischemic stroke (AIS) patients. Today, it is the accepted standard of care.<sup>[1-7]</sup> However, despite high recanalization rates (66%–94%), up to half of the patients will not present a good neurological outcome after MT.<sup>[1,8-10]</sup> In a recent meta-analysis of five randomized trials, only 46% of patients treated with MT achieved functional independence at

90 days, and approximately, 15% of patients died at 90 days posttreatment.<sup>[1]</sup>

Paradoxically, restoring blood flow saves tissue but also brings on reperfusion injury (RI).<sup>[11-14]</sup> RI can account for a significant amount of damage and depends on ischemic duration.<sup>[15-17]</sup> To further improve AIS patient outcomes, neuroprotective strategies are needed. Thus far, no neuroprotective has been implemented into standard AIS patient care.<sup>[18]</sup>

Therapeutic hypothermia (TH) is perhaps the most robust neuroprotectant studied preclinically.<sup>[12,19]</sup> TH regulates numerous pathways involved in the evolution of

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**How to cite this article:** Merrill TL, Smith BF, Mitchell JE, Merrill DR, Pukenas BA, Konstas AA. Infusion warm during selective hypothermia in acute ischemic stroke. *Brain Circ* 2019;5:218-24.

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Submission: 22-10-2019  
Revised: 28-10-2019  
Accepted: 14-11-2019

ischemic stroke showing benefit in animal models.<sup>[19-24]</sup> Moreover, its effects are multimechanistic, impacting an immense repertoire of metabolic and molecular cell death mechanisms, including suppressing free radical production, limiting inflammatory mediators, modifying ischemia-mediated calcium influx, and reducing blood-brain barrier disruption.<sup>[19,20,25-27]</sup> In a meta-analysis of over 100 published preclinical studies, the greatest tissue salvage efficacy was associated with cooler tissue temperatures ( $<31^{\circ}\text{C}$ ) when initiated early-before or at onset of ischemia.<sup>[20]</sup>

This paper explores selective TH via intracarotid saline infusion cooling.<sup>[21,28]</sup> We specifically sought to quantify warming effects that can reduce the effectiveness or potency of this technique. Using an *in vitro* study, we seek to answer these fundamental questions. Where does the warming effect occur and to what extent? What are the dynamics of this warming? How do single infusion catheters and two coaxial catheters compare? Finally, what is the predicted impact of these warming effects of brain tissue cooling dynamics?

## Materials and Methods

Our work focused on selective hypothermia, exploring the impact of infusion warming effects on predicted brain cooling dynamics. The *in vitro* infusion setup [Figure 1] was selected to be similar to prior brain cooling clinical studies.<sup>[28,29]</sup> The independent variables were saline infusion flow rate, catheter configuration (single or two coaxial), and IV bag insulation (insulated or uninsulated). Fixed variables included IV bag type, aorta and internal carotid flow rate, IV bag initial exit temperature,

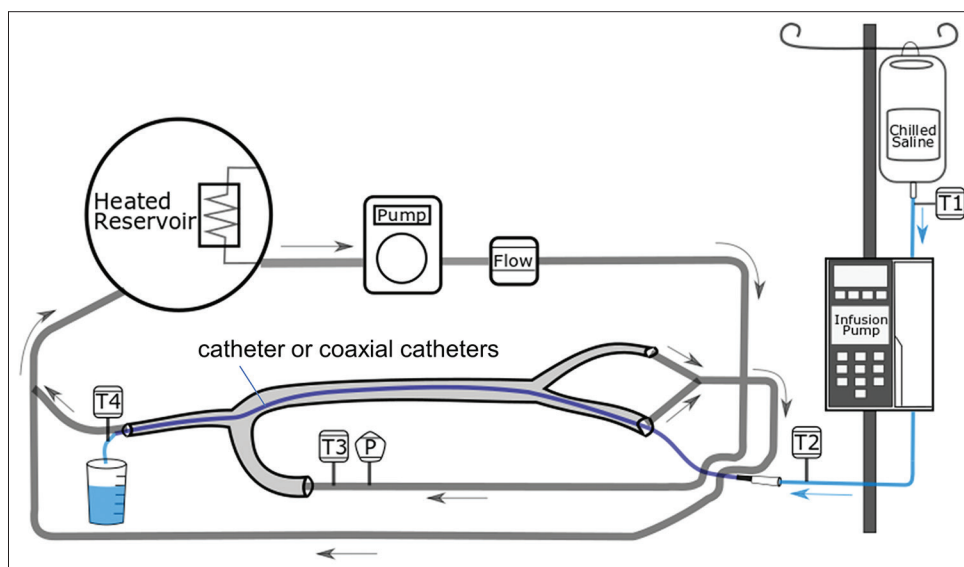
infusion duration, and systemic temperature. Dependent variables measured over the infusion duration were IV bag exit temperature and catheter inlet and exit temperature. Brain cooling temperature response was predicted based, in part, on measured catheter exit temperatures and flow rates.

## Materials and preparation

Distilled water was used instead of 0.9% isotonic saline for ease of use. Distilled water and saline have nearly identical thermal fluid properties. The freeze point for distilled water is  $0^{\circ}\text{C}$ , for isotonic saline, it is  $-0.53^{\circ}\text{C}$ .<sup>[30]</sup> Two common interventional devices were used a 5.5F Penumbra Select and 8F Stryker FlowGate Balloon Guide Catheter. Standard 1 L IV bags from Baxter (Deerfield, Chicago, IL, USA) were used together with a Baxter two-channel infusion pump. Baxter standard infusion line tubing (ILT) was used with both channels. To insulate the IV bag, we used a pressure infuser bag from Emergency Medical Products, Inc., Dublin OH. A Hotpoint freezer (General Electric, Boston, MA, USA) was used to cool and store the IV bags prior to use. All temperature probes were calibrated to  $\pm 0.3^{\circ}\text{C}$  using an resistance temperature detector temperature probe (Cole Parmer, Vernon Hills, Chicago, IL, USA). Flow rates were calibrated gravimetrically to  $\pm 0.6\text{ ml/min}$  for the carotid flow and  $\pm 50\text{ ml/min}$  for the aortic flow. Each temperature sensor was T-type thermal couple (Physitemp, Clifton, NJ, USA) placed in T-junction plastic fittings with insulation to avoid immersion errors.<sup>[31]</sup>

## Testing protocol

To carefully explore warming effects during intracarotid cooling, a mock circulatory loop previously described,



**Figure 1:** Mock loop used to simulate thermal fluid conditions in the human cardiovascular system. “T” and “P” represent temperature and pressure sensors. Warm distilled water is circulated throughout. Cold infusion of distilled water enters at the femoral artery location through the proximal port of an interventional device, eventually emerging from the distal tip located in the internal carotid artery. Temperatures T1, T2, and T4 are presented in Tables 1, Figures 2 and 3

and an infusion system was used [Figure 1].<sup>[32]</sup> This mock loop creates steady flow conditions since time-averaged pulsatile flow heat transfer coefficients are equivalent.<sup>[33]</sup> A LabView program (National Instruments, Austin, TX, USA) was used to continuously monitor flows and temperatures at a sampling rate of 1 Hz. Four flow rate settings on the Baxter two-channel infusion pump were chosen 10, 20, 30, and 40 ml/min based on prior clinical studies.<sup>[28,34]</sup> Actual flow rates, measured gravimetrically were less due to catheter configuration flow resistance.<sup>[35]</sup> Aorta and internal carotid artery (ICA) flow were maintained at  $3,500 \pm 200$  ml/min and  $240 \pm 30$  ml/min, respectively. Two catheter configurations were used, single catheter and two coaxial catheters and two IV bag configurations were chosen, insulated and noninsulated. Coaxial catheters have additional insulation along the catheter shaft due to the surrounding outer catheter and the annulus of stagnant blood or infusate. In the end, a total of 16 different tests (4 flows \*2 catheter configurations \*2 IV bag config.) were done in triplicate.

With the mock loop at a steady-state temperature of  $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ , a chilled IV bag was taken from the freezer and connected to the infusion pump and the inserted catheter configuration using the ILT. With leak-free and deaired connections in place, the infusion pump was activated at one of the four prescribed flow rate settings and continued for a duration of 20 min, a value similar to previous clinical studies.<sup>[28,29]</sup> To ensure initial condition equivalence for this inherently transient thermal process (the IV bag temperature is not fixed), data capture commenced when the IV bag exit temperature reached  $4^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . Data capture of all independent, fixed, and dependent variables were taken at one sample per second using a LabView program (National Instruments, Austin, TX, USA) and stored for postprocessing with Excel (Microsoft Inc., Redmond, WA, USA) and Matlab (Mathworks Inc., Natick, MA, USA).

### Brain tissue cooling predictions

Predicted brain tissue dynamics was based on previous research for brain tissue cooling directly distal to an occlusion in the middle cerebral artery (MCA).<sup>[36]</sup> In their study, the Pennes' bioheat equation was used assuming that the metabolic rate was negligible, and conductive heat transport into the cooled tissue was negligible. The only flow delivered to the tissue in this study was microcatheter delivered cooled saline. For our study, we have assumed a total mass of interest of 300 g surrounding the MCA with no metabolic heat generation and an initial temperature of  $37^{\circ}\text{C}$ .<sup>[37,38]</sup> We assume the ICA is approximately 8.5 cm long and the inner diameter is 4.8 mm.<sup>[39,40]</sup> We also assume cooling occurs proximal to a MCA without an occlusion. In this

case, we assume the brain arteries are autoregulated with a total flow rate (saline infused + blood) in the ICA of 240 ml/min with approximately 50% traveling to the region of interest in the MCA.<sup>[41,42]</sup> Ultimately, the mixed temperature (saline infused + blood) arrives at the region of interest and is used to predict brain tissue cooling.

### Analysis

Measured data for all temperatures, IV bag exit, catheter inlet, and catheter outlet are presented as means  $\pm$  standard deviation. To compare mean values, an ANOVA was used with a Tukey–Kramer honestly significant difference (HSD) *post hoc* test. JMP Pro 15 (SAS Institute, Cary, North Carolina, USA) was applied.

## Results

We studied a total of four different infusion layouts ranging from *least likely* to reduce warming effects to *most likely* to reduce warming effects:

- Layout 1 – single catheter with uninsulated IV bag
- Layout 2 – single catheter with insulated IV bag
- Layout 3 – two coaxial catheters with uninsulated IV bag
- Layout 4 – two coaxial catheters with insulated bag.

Distilled water temperatures (T1-T4, [Figure 1]) in degrees Celsius and flow rate in ml/min were recorded for each layout over a 20-min infusion duration.

Table 1 shows a direct comparison for all the layouts at maximum flow at the end of testing. Despite the advantage of an insulated IV bag, the impact on the final delivery temperature is small,  $<1^{\circ}$ . This outcome was true for all flow rates. The dominant warming process occurs along with the catheter configuration. The coaxial catheter configurations provide approximately  $4^{\circ}\text{C}$  cooler catheter outlet temperatures compared with single catheter configurations. ANOVA and Tukey–Kramer HSD tests showed that the coaxial catheter Layouts (#3 and #4) are significantly different than single catheter Layouts (#1 and #2).

Exploring Layout 1 outcomes, testing [Figure 2] showed that the dominant warming occurs inside the catheter, as

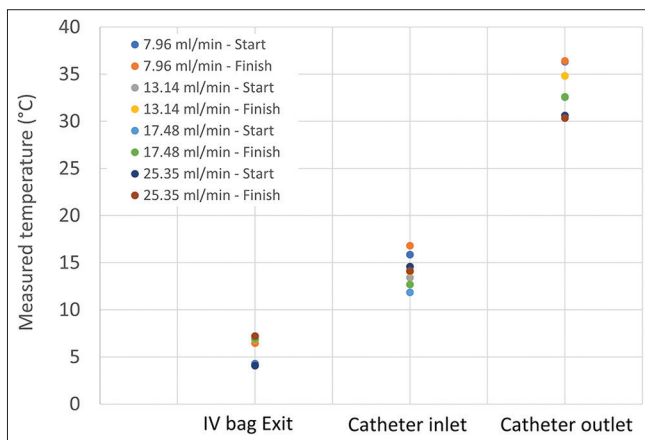
**Table 1: Average intravenous bag outlet, catheter inlet, and catheter outlet temperatures in degrees Celsius for four different layouts at a flow rate of  $25.0 \pm 0.5$  ml/min after a 20-min infusion duration**

	Single catheter		Two coaxial catheters	
	Uninsulated	Insulated	Uninsulated	Insulated
Location	Layout 1	Layout 2	Layout 3	Layout 4
IV bag outlet	7.22 $\pm$ 0.53	5.30 $\pm$ 0.24	7.72 $\pm$ 0.29	5.60 $\pm$ 0.53
Catheter inlet	14.13 $\pm$ 0.55	12.66 $\pm$ 0.19	13.73 $\pm$ 0.27	13.69 $\pm$ 0.18
Catheter outlet	30.34 $\pm$ 0.49	30.56 $\pm$ 0.14	25.96 $\pm$ 0.15	26.39 $\pm$ 0.34

the chilled infusion enters the proximal hub and exits the distal tip. After 20 min of infusion, the average warming along the catheter was  $19.12^{\circ}\text{C} \pm 2.00^{\circ}\text{C}$ , whereas the average warming along the ILT was  $7.56^{\circ} \pm 1.95^{\circ}\text{C}$ . Said differently, the percentage warming along the catheter – defined as the temperature increase along the catheter divided by the total temperature rise (Catheter out–IV bag exit) \*100% – was  $72\% \pm 5\%$ , considering all flow rates. Along the ILT in Layout 1, the percentage warming was  $28\% \pm 5\%$ , considering all flow rates.

Exploring Layout 4 outcomes, testing [Figure 3] again showed that the dominant warming occurs inside the catheter, as the chilled infusion enters the proximal hub and exits the distal tip. After 20 min of infusion, the average warming along the catheter was  $16.89^{\circ}\text{C} \pm 2.97^{\circ}\text{C}$ , whereas the average warming along the ILT was  $8.73^{\circ}\text{C} \pm 2.16^{\circ}\text{C}$ . Said differently, the percentage warming along the catheter – defined as the temperature increase along the catheter divided by the total temperature rise (Catheter out–IV bag exit) \*100% – was  $66\% \pm 5\%$  considering all flow rates. Along the ILT in Layout 4, the percentage warming was  $34\% \pm 5\%$ , considering all flow rates.

In terms of warming as a function of time, only the IV bag experienced temperature elevations  $>1^{\circ}$  over 20 min or  $>3^{\circ}\text{C}/\text{h}$ . For Layout 1 with the uninsulated bag, the average temperature rise was  $2.72^{\circ}\text{C} \pm 0.39^{\circ}\text{C}$  in 20 min. As expected for Layout 4 with the insulated bag, the average temperature rise was decreased significantly  $1.10^{\circ}\text{C} \pm 0.58^{\circ}\text{C}$  over 20 min. Because the thermal mass (mass \* specific heat) of the IV bag is reduced more quickly with higher flow rates, the infusate remaining in the IV bag experiences more temperature change over time, regardless of layout.



**Figure 2:** Layout 1 measured temperature at four flow rates at the start and finish of infusion. Measurements were taken in triplicate at the start and finish of a 20 min duration for all flow rates. The average standard deviation in temperature was  $0.48^{\circ}\text{C}$ , with a range of  $0.04^{\circ}\text{C}$ – $1.75^{\circ}\text{C}$ . The dominant rewarming occurs along the catheter pathway with the uninsulated IV bag experiencing the greatest change in temperature with time. Increasing infusion flow rates lead to lower catheter exit temperatures

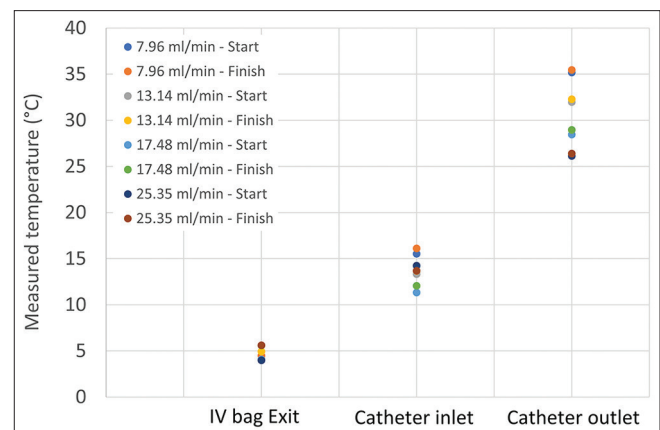
For all layouts, overall infusion warming, indicated by catheter outlet temperature, is reduced with increasing infusion flow rates. This can be explained by assuming the thermal resistances to heat transfer (catheter wall conduction, blood-side convection, and infusate-side convection) all remain constant. This is reasonable since the wall thickness and materials are constant, and the convective heat transfer coefficients are constant or nearly constant along the catheter configuration internal and external surfaces. With the resistances constant and the driving temperature difference constant ( $T_{\text{blood}} - T_{\text{distilled\_water}}$ ), the key variable impacting heat transfer to the distilled water is the amount of time and the distilled water is exposed to the warm environment. Increasing infusion flow rates reduce exposure or residence time, reducing warming effects.

Using the temperature measurements shared above and recently published work on insulated infusion systems, we applied Pennes Bioheat equation to predict brain tissue temperatures surrounding the MCA [Figure 4].<sup>[36,43]</sup> As expected Layout 1, a single catheter without an insulated IV bag at low flow revealed little or no tissue cooling. Layout 2 at the low flow also revealed little tissue cooling. Tripling the flow, both layouts cooled more deeply.

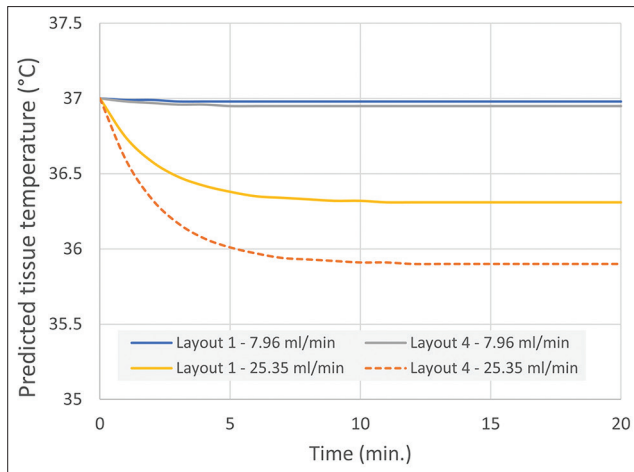
Compared with whole-body cooling systems, the coaxial catheter configuration at high flow provides rapid tissue temperature reduction of about  $1^{\circ}\text{C}$  in 5 min or  $12^{\circ}\text{C}/\text{h}$ .

## Discussion

Our study reveals a number of important outcomes for clinical application of selective hypothermia for AIS. While numerous other studies have looked at warming



**Figure 3:** Layout 4 measured temperature at four flow rates at the start and finish of infusion. Measurements were taken in triplicate at the start and finish of a 20 min duration for all flow rates. The average standard deviation in temperature was  $0.40^{\circ}\text{C}$ , with a range of  $0.03^{\circ}\text{C}$ – $1.05^{\circ}\text{C}$ . Similar to Layout 1 – the dominant rewarming occurs along the catheter pathway



**Figure 4:** Predicted brain tissue behavior in the middle cerebral artery. Using measured data shown in Figures 2 and 3, brain tissue temperature dynamics surrounding the middle cerebral artery were predicted.<sup>[43]</sup> Sharply increasing the infusion flow rates led to a maximum tissue cooling rate of approximately 1°C/5 min or 12°C/h

of infusate outside the human body, tubing, and IV bags, few researchers have looked at the entire pathway for IV bag to delivery deep inside the human body with catheters.

First, there appears to be an underappreciation for the warming effect break down during the application of selective hypothermia for AIS. From this study, with its limitations noted below, it is reasonable to conclude that approximately two-thirds or more of the total warming from IV bag to location of brain injury occurs along the catheter or coaxial catheter configuration. A third or less of the total warming takes place in the ILT that connects the IV bag to the catheter while passing through an infusion pump.

Second, insulation can help reduce warming significantly. Insulating the IV bag becomes more important as infusion rates increase. Higher infusion rates drain the bag more quickly leaving less thermal mass inside the IV bag, making it more prone to warming. Other researchers confirmed this behavior as well looking at 12 different application regimes (various IV bag volumes and flow rates).<sup>[44]</sup> In our study, IV bag insulation had virtually no impact on catheter exit or delivery temperatures. Again, at high flow rates, this would likely change and bring on the need for IV bag insulation.

Overall, our IV bag results are in line with previous findings where rate of 1 L IV bag warming at flow rates of 48.2 ml/min  $\pm$  3.7 ml/min was not rapid with or without insulation.<sup>[45]</sup> Other researchers have also taken a step farther and have explored inserting ice packs into insulating sleeves to maximize cooling effect and reduce warming.<sup>[46,47]</sup>

Third, the ILT and the catheter offer the greatest return for insulative approaches. Previous work, motivated by the use of TH for cardiac arrest victim, used normal saline at 4°C at 30 ml/min and 15 ml/min to clearly identify that the ILT was a major culprit in limiting effective TH.<sup>[48]</sup> To reduce ILT warming, this group applied cold packs to a coiled ILT. Another team of researchers exploring whole-body cooling, not selective brain cooling, used household aluminum foil to insulate the ILT for flow rates ranging from 10 to 100 ml/min, showing dramatic reducing in ILT warming.<sup>[47]</sup> They stated that the aluminum foil provides two methods for insulation: reflecting thermal radiation from the environment and limiting thermal conduction by trapping air pockets around the tubing.

In terms of catheter insulation, a recent preclinical study, based on previous theoretical models for intracarotid cooling with insulative infusion systems, showed significant tissue reductions and subsequent infarct size reductions.<sup>[43,49]</sup> At the same time, regardless of the layout used, cooler delivery temperatures and more rapid tissue cooling could be achieved with higher infusion rates. Organ perfusion overload and hemodilution remain clinical safety concerns for improved performance with higher infusion rates. Insulative systems may enable optimal cooling while reducing patient safety risks.

### Limitations

Our study was conducted under a controlled environment in terms of consistent surrounding temperature and humidity levels. There were no random patients or end-user events that could potentially increase warming effects such as intermittent infusion, holding the infusion line or IV bag, and beginning an infusion with a small volume of infusate. The number of catheter configurations was also small considering the volume of potential catheters that could be explored. This same limitation is also true for the number of flow rates examined and the range of IV bag volumes studied.

### Conclusion

In light of this work, previous work done in this area using flow rates around 10 ml/min will likely not cool tissue significantly (0.1°C or less).<sup>[34]</sup> At the same time, significant cooling could be possible if the cooling was done distal to an occlusion where no blood mixing occurred with the infusate exiting a delivery catheter.<sup>[28]</sup> Higher infusion flow rates can produce rapid tissue cooling relative to whole-body cooling systems; however, the depth will likely be close to 1.0°C at the maximum flows studied here. Continued research in this area of selective hypothermia of AIS should carefully consider predicted brain tissue temperature dynamics, in terms of target temperature and time to reach the target

temperature, before selecting their infusion system and their infusion flow rates.

### Financial support and sponsorship

We gratefully acknowledge the support of NIH Grant # 5R25EB014782-05. The content is solely the responsibility of the authors and does not reflect the opinions of the sponsors.

### Conflicts of interest

TL Merrill, JE Mitchell, and DR Merrill are all employees of FocalCool, LLC, a company developing brain cooling technology.

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