


## ORIGINAL ARTICLE

# The intra-arterial selective cooling infusion system: A mathematical temperature analysis and in vitro experiments for acute ischemic stroke therapy

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## Abstract

**Introduction:** The neuroprotection of acute ischemic stroke patients can be achieved by intra-arterial selective cooling infusion using cold saline, which can decrease brain temperature without influencing the body core temperature. This approach can lead to high burdens on the heart and decreased hematocrit in the scenario of loading a high amount of liquid for longtime usage. Therefore, autologous blood is utilized as perfusate to circumvent those side effects.

**Methods:** In this study, a prototype instrument with an autologous blood cooling system was developed and further evaluated by a mathematical model for brain temperature estimation.

**Results:** Hypothermia could be achieved due to the adequate cooling capacity of the prototype system, which could provide the lowest cooling temperature into the blood vessel of 10.5°C at 25 rpm (209.7 ± 0.8 ml/min). And, the core body temperature did not alter significantly (-0.7 ~ -0.2°C) after 1-h perfusion. The cooling rate and temperature distributions of the brain were analyzed, which showed a 2°C decrease within the initial 5 min infusion by 44 ml/min and 13.7°C perfusate.

**Conclusion:** This prototype instrument system could safely cool simulated blood in vitro and reperfuse it to the target cerebral blood vessel. This technique could promote the clinical application of an autologous blood perfusion system for stroke therapy.

## KEYWORDS

autologous blood, ischemic stroke, numerical analysis, prototype instrument, therapeutic hypothermia

Miaowen Jiang and Ming Li contributed equally to this work.

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## 1 | INTRODUCTION

Stroke is one of the leading causes of mortality and disability worldwide.<sup>1</sup> Acute ischemic stroke (AIS) accounts for approximately 80% of all strokes.<sup>2</sup> The clinical prognosis of patients with AIS can be improved by vascular recanalization via intravenous thrombolysis or mechanical thrombectomy to restore cerebral blood perfusion of the ischemic brain region.<sup>3</sup> However, vascular recanalization does not guarantee a positive outcome. More than 80% of patients with acute occlusion of large cerebral arteries cannot be recanalized by using those endovascular techniques, but over 70% of patients die or remain disabled for the rest of their lives.<sup>4,5</sup> This can be solved by using neuroprotective strategies.

Therapeutic hypothermia (TH) is one of the well-researched, effective, and promising neuroprotective strategies for AIS therapy. It is also the only effective neuroprotective treatment in patients with hypoxic brain injury following cardiac arrest.<sup>6,7</sup> Systemic hypothermia such as surface cooling lowers both the brain temperature and core body temperature. The drop in core body temperature causes a cascade of negative side effects that counteract the hypothermia treatment's efficacy<sup>8</sup>, such as pneumonia (40%), electrolyte problems (50%), and arrhythmias and heart failure (80%), which has limited the application of systemic hypothermia for AIS treatment.<sup>9</sup> As a result, local hypothermia by selective brain cooling (SBC) has evolved into a viable and promising neuroprotective treatment.<sup>10</sup>

In the previous study, our group employed targeted local hypothermia in brain tissues of MCAO rodent animal models by intra-arterial selective cooling saline infusion (IA-SCI), which decreased cerebral infarction volume and enhanced neurological performance.<sup>11,12</sup> Then, in a non-human primate model of embolic stroke, we found that IA-SCI improved its long-term neurological outcomes.<sup>13</sup> And in clinical investigations, we verified that IA-SCI was safe<sup>14</sup> and could further reduce the expansion of cerebral infarction AIS patients on the basis of intravascular thrombolysis or mechanical thrombectomy.<sup>15</sup> Except for its beneficial effects, the current dilemma of IA-SCI is that it will increase body fluid volume, can increase heart strain and lower hematocrit, and cannot be exploited for long-term usage.<sup>8</sup>

Using cold autologous blood instead of normal saline under cardiopulmonary bypass is an appropriate way of solving the abovementioned negative effects of IA-SCI.<sup>16</sup> In a rat model of cerebral infarction, we have preliminarily shown that the intra-arterial selective cooling autogenous blood infusion (IA-SCAI) is both safe and efficacious.<sup>17</sup>

Currently, there are currently no autologous blood cooling infusion systems designed specifically in clinical for cerebral hypothermia therapy, and the optimized hypothermic perfusion parameters are unavailable. In order to achieve clinical transformation and long-term targeted local hypothermia maintenance of IA-SCAI, a prototype instrument system for IA-SCAI was designed and constructed in this study, which consisted of hemodynamic driver, heat exchanger, extracorporeal circulation lines, and monitoring devices. For the purpose of evaluating the cooling effect

during the process of IA-SCAI by using this system, a brain temperature estimation of hemodynamics and biological heat transfer based on numerical simulations and in vitro experiments were also proposed. The temperature of cold autogenous blood in the IA-SCAI system at varied flow rates was acquired through an arterial analog vascular system, which was built by three-dimensional (3D) modeling and 3D-printing technology.

Based on the Pennes' biological heat transfer mathematical model,<sup>18</sup> some optimized mathematical models were used to evaluate and predict brain temperature and its influencing factors under the condition of different hypothermia therapy methods.<sup>19-24</sup> In this study, perfusion flow rates, metabolism-produced heat, and brain tissue depth were taken into consideration during the simulation. We obtained temperature response curves with different cooling power and cooling time and confirmed the feasibility of the approach in the treatment of hypothermia for AIS therapy by using the IA-SCAI prototype instrument system.

## 2 | MATERIALS AND METHODS

### 2.1 | The IA-SCAI prototype instrument system

Based on extracorporeal circulation technology, in this IA-SCAI hypothermia system, the patient's autologous blood is exported from the femoral artery using a blood pump, then it is cooled by a heat exchanger, and reperfused into the target brain tissue via the internal carotid artery (ICA). (Figure 1A) A customized circulation device is used to duplicate the IA-SCAI process, which includes a blood peristaltic pump (MP300; Prefluid), blood heat exchanger (MYOthem XP; Medtronic), cooling water tank (T1; Auwii), extracorporeal circuit, an intervention cooling catheter (Codman ENVOY® Catheter, 5F), temperature sensors (HEL-705-U-1-12-00; Honeywell), blood pressure sensors (ABPDANN160KGAA5; Honeywell), and flow-bubble sensors (CO.56; Sonotec). (Figure 1B).

### 2.2 | Theoretical model for brain temperature prediction

In the event of restricted nondestructive intracranial temperature monitoring methods, theoretical computational modeling of brain tissue thermal analysis has become a significant tool for predicting brain tissue temperature in IA-SCAI. The Pennes' bioheat biological heat transfer equation may be used to calculate  $T$  for brain tissue temperature.<sup>20</sup> Heat conduction in tissue, heat generation through metabolism, and heat exchange between arterial blood and tissue are all taken into account in this equation.

$$\rho_t c_t \frac{\partial T}{\partial t} = \nabla \cdot (\lambda_t \nabla T) + \rho_b \cdot c_b \cdot \omega \cdot (T_a - T) + P_{Met} \quad (1)$$

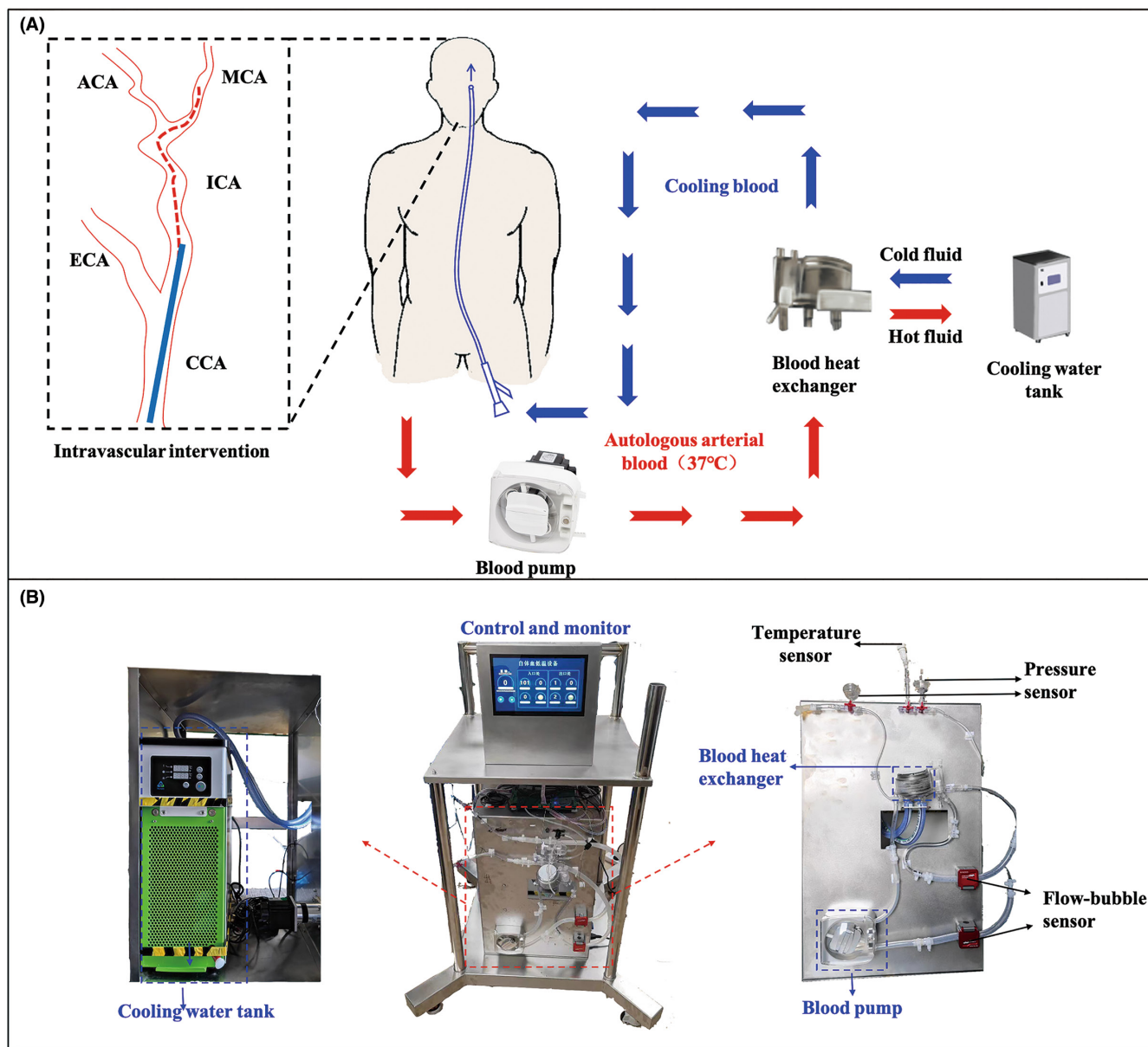


FIGURE 1 (A) Schematic diagram of the IA-SCAI process (Common carotid artery: CCA; External carotid artery: ECA; Internal carotid artery: ICA; Middle cerebral artery: MCA; Anterior cerebral artery: ACA). (B) The prototype instrument system for IA-SCAI

where  $\rho_t$  ( $\text{kg}/\text{m}^3$ ) is the tissue density;  $c_t$  ( $\text{J}/\text{Kg} \cdot \text{K}$ ) is the specific heat;  $\lambda_t$  ( $\text{W}/\text{K} \cdot \text{m}$ ) is the thermal conductivity;  $c_b$  ( $\text{J}/\text{Kg} \cdot \text{K}$ ) is the specific heat of blood;  $\rho_b$  ( $\text{kg}/\text{m}^3$ ) is the blood density;  $\omega$  ( $\text{ml}/\text{min} \cdot 100\text{g}$ ) is the perfusion rate;  $T_a$  ( $^{\circ}\text{C}$ ) is the blood temperature of the perfusion;  $P_{Met}$  ( $\text{W}/\text{m}^3$ ) is the metabolic heat of the tissue. The effect of cooling time ( $t$ ) and brain tissue depth ( $r$ ) on temperature change during IA-SCAI was investigated based on the Pennes' equation (Equation 1). The metabolic thermogenesis of brain tissue (gray matter and white matter) was taken into account in the development of a theoretical computer model (Equation 2) for brain temperature prediction.

$$\rho_t c_t \frac{\partial T}{\partial t} = \frac{\lambda_t}{r^2} \cdot \frac{\partial}{\partial r} \left( r^2 \cdot \frac{\partial T}{\partial r} \right) + \rho_b \cdot c_b \cdot \omega \cdot (T_a - T) + P_{Met} \quad (2)$$

Michenfelder and Milde et al. hypothesized that the metabolic heat generation rate dropped by a factor of 3.<sup>25</sup> Following that, Xu et al. proposed an analytical formula (Equation 3) for metabolic heat production based on brain temperature as a criterion<sup>26</sup>:

$$P_{Met} = q_0 \times 3^{0.1T-3.7} \quad (3)$$

$q_0$  is the metabolic rate of brain tissue. To solve the mathematical model (Equation 2), we employ the finite element approach and the numerical difference method:

$$\frac{\partial T}{\partial t} = \frac{T(i+1,j) - T(i,j)}{\rho_t \cdot c_t \cdot \Delta t} = \frac{1}{\rho_t \cdot c_t \cdot \Delta t} \left\{ \frac{\lambda_t}{r^2} \cdot \frac{\partial}{\partial r} \cdot \left[ r^2 \cdot \frac{\partial T(i+1,j) - \partial T(i,j)}{\partial r} \right] + \rho_b \cdot c_b \cdot \omega \cdot [T_a - T(i+1,j) + T(i,j)] + q_0 \times 3^{(0.1T-3.7)} \right\} \quad (4)$$

$$\frac{\partial T}{\partial r} = \frac{T(i,j+1) - T(i,j)}{\rho_t \cdot c_t \cdot \Delta r} = \frac{1}{\rho_t \cdot c_t \cdot \Delta r} \left\{ \frac{\lambda_t}{r^2} \cdot \frac{\partial}{\partial r} \cdot \left[ r^2 \cdot \frac{\partial T(i,j+1) - \partial T(i,j)}{\partial r} \right] + \rho_b \cdot c_b \cdot \omega \cdot [T_a - T(i,j+1) + T(i,j)] + q_0 \times 3^{(0.1T-3.7)} \right\} \quad (5)$$

$$\frac{\partial^2 T}{\partial r^2} = \frac{T(i,j+1) - 2T(i,j) + T(i,j-1)}{\rho_t \cdot c_t \cdot (\Delta r)^2} = \frac{1}{\rho_t \cdot c_t \cdot (\Delta r)^2} \left\{ \frac{\lambda_t}{r^2} \cdot \frac{\partial}{\partial r} \cdot \left[ r^2 \cdot \frac{\partial T(i,j+1) - 2\partial T(i,j) + \partial T(i,j-1)}{\partial r} \right] + \rho_b \cdot c_b \cdot \omega \cdot [T_a - T(i,j+1) + 2T(i,j) - T(i,j-1)] + q_0 \times 3^{(0.1T-3.7)} \right\} \quad (6)$$

The boundary and initial conditions become:

$$t = 0 \text{ s}, r = 0 \text{ cm}, T = 37^\circ \text{ C} \quad (7)$$

$$r = 0 \text{ cm}, T = 37^\circ \text{ C} \quad (8)$$

$$r = (0 \text{ cm}, 10 \text{ cm}) \quad (9)$$

All data analysis and numerical simulations were performed in Matlab (Natick, MA). For the temperature calculation, Table 1 presents an overview of all fixed parameters and their values from references<sup>20,27</sup>.

### 2.3 | Experimental study on in vitro simulation

In order to obtain the blood temperature  $T_a$  ( $^\circ\text{C}$ ) of the perfusion by the IA-SCAI prototype instrument system, experiments were carried out on a 1:1 3D-printed physical cerebral vascular model (Preclinic Medical, Shanghai, China) which was filled with simulated blood (56 % glycerin and 44 % bi-distilled water,<sup>28</sup> 37 $^\circ\text{C}$ ). (Figure 2) A pulsing

pump (pulsation frequency: 80 beats/min, flow range of the pump: 0–1000 ml/min) and a constant temperature (37 $^\circ\text{C}$ ) water tank powered the circulatory in the cerebral vascular model. To acquire the flow of

simulated blood within the carotid artery (CCA), we may change the flow of this circulatory pump (injected into the aortic arch, as illustrated in Figure 2A). We employed an interventional catheter (Codman ENVOY<sup>®</sup> Catheter, 5F) to simulate the IA-SCAI pathway in the cerebral vascular model with the prototype instrument system in vitro.

A thermocouple K-type multichannel temperature tester (AT4204; Apilent) was used to monitor the cerebral vascular temperatures in different positions of the model (cold autologous blood inflow temperature at the femoral ( $T_{\text{infusion}}$ ), temperature at ICA ( $T_{\text{ICA}}$ ), and MCA ( $T_{\text{MCA}}$ )). The MCA segment was thought to be the site of cerebral ischemia infarctions. The temperature in the aorta can be equivalent to the core temperature of the human body ( $T_{\text{Body}}$ ) during the IA-SCAI process. The K-type thermocouple was placed into the cerebral vascular model (Figure 2B) through a hemostatic valve and calibrated to 0.1 $^\circ\text{C}$  throughout a temperature range of –50.0 to 250.0 $^\circ\text{C}$ . The room temperature during the in vitro experiment was about 20.0 $^\circ\text{C}$ , whereas the temperature of the cerebral vascular model was kept at 36.3 $\pm$ 0.1 $^\circ\text{C}$ , and the cooling water tank temperature was set at 5.0 $\pm$ 0.2 $^\circ\text{C}$ . The CCA flow inside the in vitro experiment was set to 180 ml/min to conform with the parameters of cerebral blood flow in patients with AIS because blood perfusion in the developing infarct (ischemic penumbra) was lowered to 40%–50% (based on normal 400 ml/min).<sup>20,29,30</sup>

TABLE 1 The partial physiological parameters of the human body

Parameter	Symbol	Value
Blood density	$\rho_b$	1050 kg / m <sup>3</sup>
Blood-specific heat capacity	$c_b$	3800 J / Kg · K
Blood thermal conductivity	$\lambda_b$	0.5 W / m · K
Tissue density	$\rho_t$	1030 kg / m <sup>3</sup>
Tissue-specific heat capacity	$c_t$	3700 J / Kg · K
Tissue thermal conductivity	$\lambda_t$	0.49 W / m · K
Perfusion rate of gray matter	$\omega_{\text{gray}}$	80 ml / min · 100 g
Perfusion rate of white matter	$\omega_{\text{white}}$	20 ml / min · 100 g
Metabolic rate of gray matter	$q_{\text{gray}}$	16,700 W / m <sup>3</sup>
Metabolic rate of white matter	$q_{\text{white}}$	4175 W / m <sup>3</sup>

### 3 | RESULTS

Using the prototype instrument system, Figure 3 summarizes the temperatures of autologous blood at the input of the femoral artery ( $T_{\text{infusion}}$ ), ICA ( $T_{\text{ICA}}$ ), MCA ( $T_{\text{MCA}}$ ), and the change in the core body temperature ( $\Delta T_{\text{Body}}$ ) of the cerebral vascular model at varied flow rates. These data were utilized to calculate and analyze the brain tissue temperature for the IA-SCAI. Higher flow rates resulted in lower temperatures of autologous blood, and the core body temperature did not alter significantly (–0.7 ~ +0.2 $^\circ\text{C}$ ) after 1-h perfusion. Hypothermia is generally accepted that a core body temperature of <35 $^\circ\text{C}$ . This can then be further subdivided into mild (32 ~ 35 $^\circ\text{C}$ ), moderate (28 ~ 32 $^\circ\text{C}$ ), and severe (<28 $^\circ\text{C}$ ) hypothermia.<sup>31</sup> Through the prototype instrument,

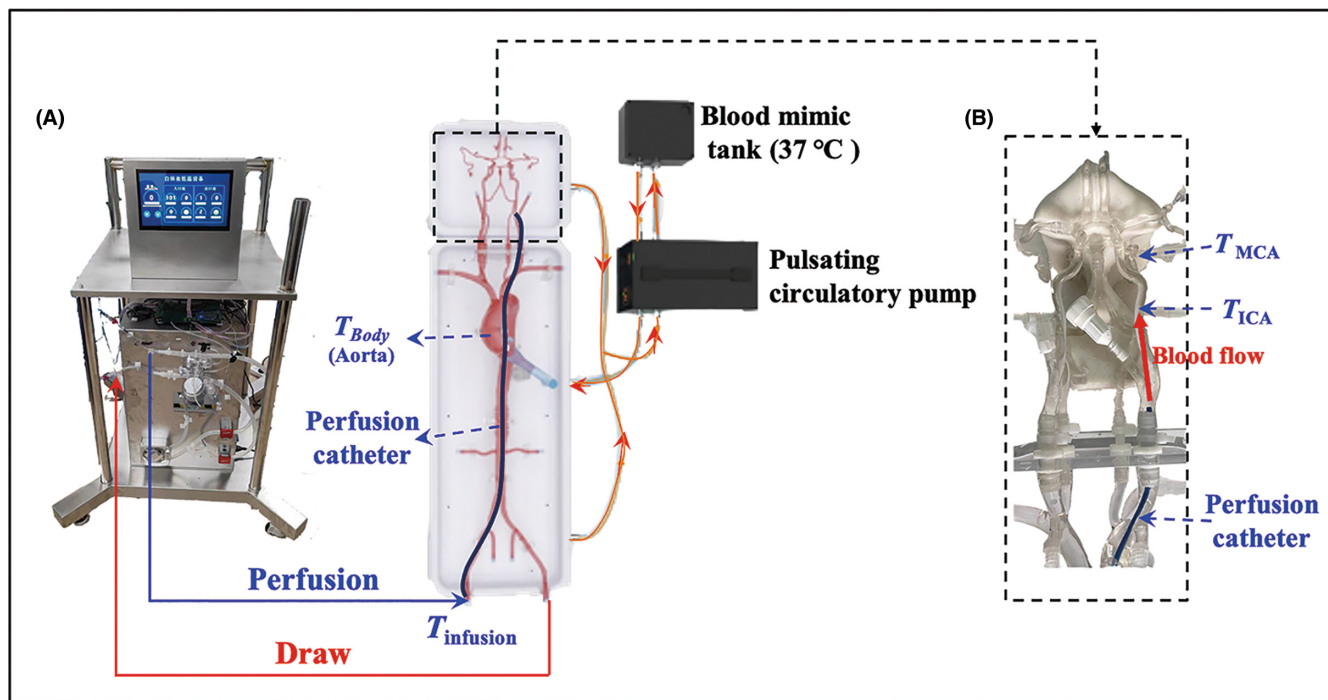


FIGURE 2 (A) The cerebral vascular model included 3D-printing blood arteries, a blood mimic sink, and a pulsing circulatory pump; (B) temperatures ( $T_{\text{infusion}}$ ,  $T_{\text{ICA}}$ , and  $T_{\text{MCA}}$ ) were evaluated inside the in vitro experiment

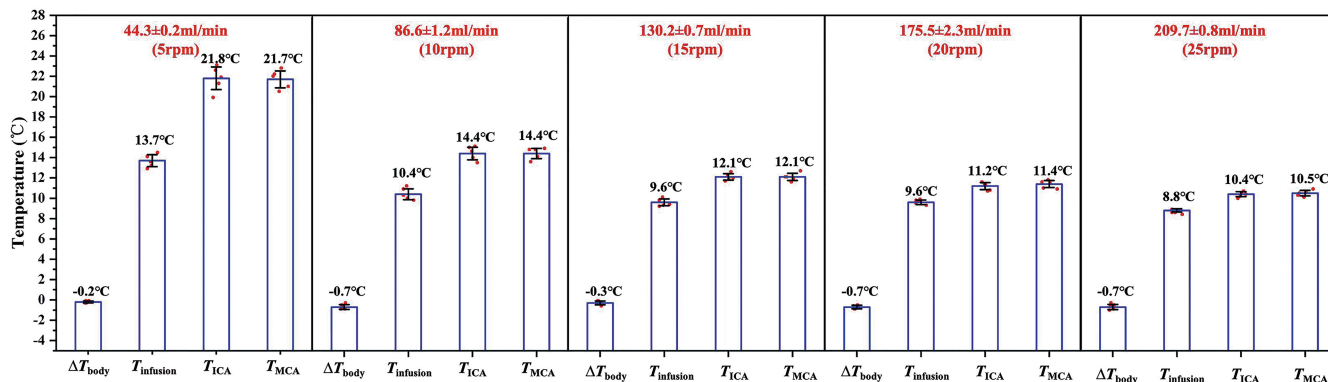
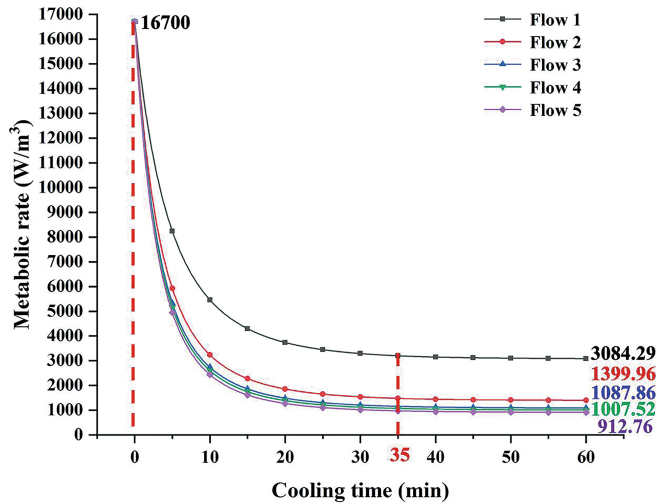


FIGURE 3  $T_{\text{infusion}}$ ,  $T_{\text{ICA}}$ ,  $T_{\text{MCA}}$ , and  $\Delta T_{\text{body}}$  temperatures at various rotation speeds of the blood pump (5 rpm, 10 rpm, 15 rpm, 20 rpm, and 25 rpm correspond to  $44.3 \pm 0.2$  ml/min (flow1),  $86.6 \pm 1.2$  ml/min (flow2),  $130.2 \pm 0.7$  ml/min (flow3),  $175.5 \pm 2.3$  ml/min (flow4), and  $209.7 \pm 0.8$  ml/min (flow5), respectively)

changing the volume of perfusion and the heat transfer efficiency of the cooling water tank could accomplish different targeted cerebral vascular temperatures. To keep the  $T_{\text{MCA}}$  temperature between 32°C and 35°C, the rotation speed can be reduced to 2~3 rpm or the cooling tank temperature set to 9~10°C.  $T_{\text{infusion}}$  dropped from 13.7 to 8.8°C and  $T_{\text{ICA}}$  dropped from 21.8 to 10.4 as the perfusion flow rose from 44.3 ml/min to 209.7 ml/min, and the temperature change of  $T_{\text{MCA}}$  was similar to  $T_{\text{ICA}}$ . Due to the inverse relationship between total heat transfer and flow rate, heat transmission decreases as flow rate increases. All different hyperthermia (mild, moderate, and severe) could be achieved due to the adequate cooling capacity of the prototype with the lowest cooling temperature into the blood vessel of 10.5°C at 25 rpm ( $209.7 \pm 0.8$  ml/min).

In addition to heat conduction between blood and brain tissue,<sup>31-33</sup> metabolic heat production of white matter (WM) and gray matter (GM) has effects on brain temperature.<sup>34</sup> Specifically, neuron-rich GM requires 2.5 times more ATP than WM,<sup>35</sup> and the baseline metabolic rate of the GM and WM of the brain at 37°C is  $16,700 \text{ W/m}^3$  and  $4175 \text{ W/m}^3$ , respectively.<sup>20</sup> Figure 4(a-b) shows the influence of different autologous blood infusion rates on the metabolic rate of the GM and WM. As shown in Figure 4(a-b), high infusion rates resulted in a faster metabolic rate, and the metabolic rate under the condition of the highest flow ( $209.7 \pm 0.8$  ml/min) were reached to  $912.76 \text{ W/m}^3$  for GM and  $403.91 \text{ W/m}^3$  for WM within 1 h, respectively. The metabolic rate of GM decreased quicker than WM. After 35 minutes of cooling, the gray matter achieved its

## (A) Gray matter



## (B) White matter

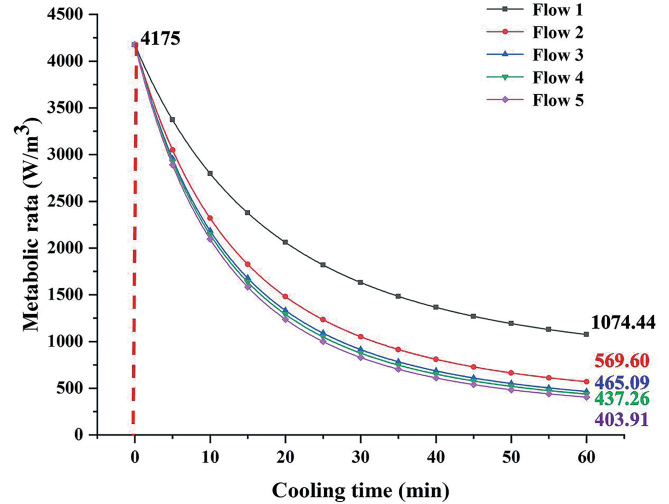


FIGURE 4 Effect of autologous blood infusion rates on the metabolic rate of the GM (A) and white (B) WM of the brain

low stable metabolic rate, whereas the white matter continued to decline after 1 hour of cooling.

The combined impact of cooling duration infusion (within 60 min) and brain tissue depth (within 10 cm) on the temperature reduction of the brain tissue is shown in Figure 5A. Faster infusion rates resulted in quicker hypothermia onset and lower brain temperatures. After a 60-min cooling infusion, the temperature of GM eventually tended to be stable at MCA ( $T_{MCA}$ ), whereas the temperature of the WM continued to decline. Compared with WM, the temperature change of GM was more obvious under different perfusion flow, for example, an infusion rate of  $209.7 \pm 0.8$  ml/min (flow 5) resulted in a minimum temperature of  $10.5^\circ\text{C}$  at the GM. Between flow 1 and flow 5, the transient temperature of GM was  $3\text{--}5^\circ\text{C}$  greater than that of WM. Mild-to-moderate hypothermia ( $35^\circ\text{C}$ ) was established in the GM within 1.3 min, which was faster than the WM (within 5 min) for the autologous blood infusion rate of flow 1, as shown in Figure 5B. As the flow increased, it took less time to reach the hypothermia temperature and had a shorter period of mild hypothermia ( $32\text{--}35^\circ\text{C}$ ) on the brain tissue, resulting in GM having a shorter duration (2.4 min by flow 1) of mild hypothermia than WM (9.5 min by flow 1).

The temperature distribution after 60 minutes of autologous blood is also shown in Figure 5A. The temperature of the brain fluctuated little under steady-state circumstances, but near the outer boundary of the brain, the temperature started to approach  $20^\circ\text{C}$  (the boundary temperature).  $T_{MCA} = 32^\circ\text{C}$  could be used to induce long-term hypothermia perfusion of autologous blood, as demonstrated in Figure 5c-d, where gray matter reached mild-to-moderate hypothermia 14.2 min before white matter.

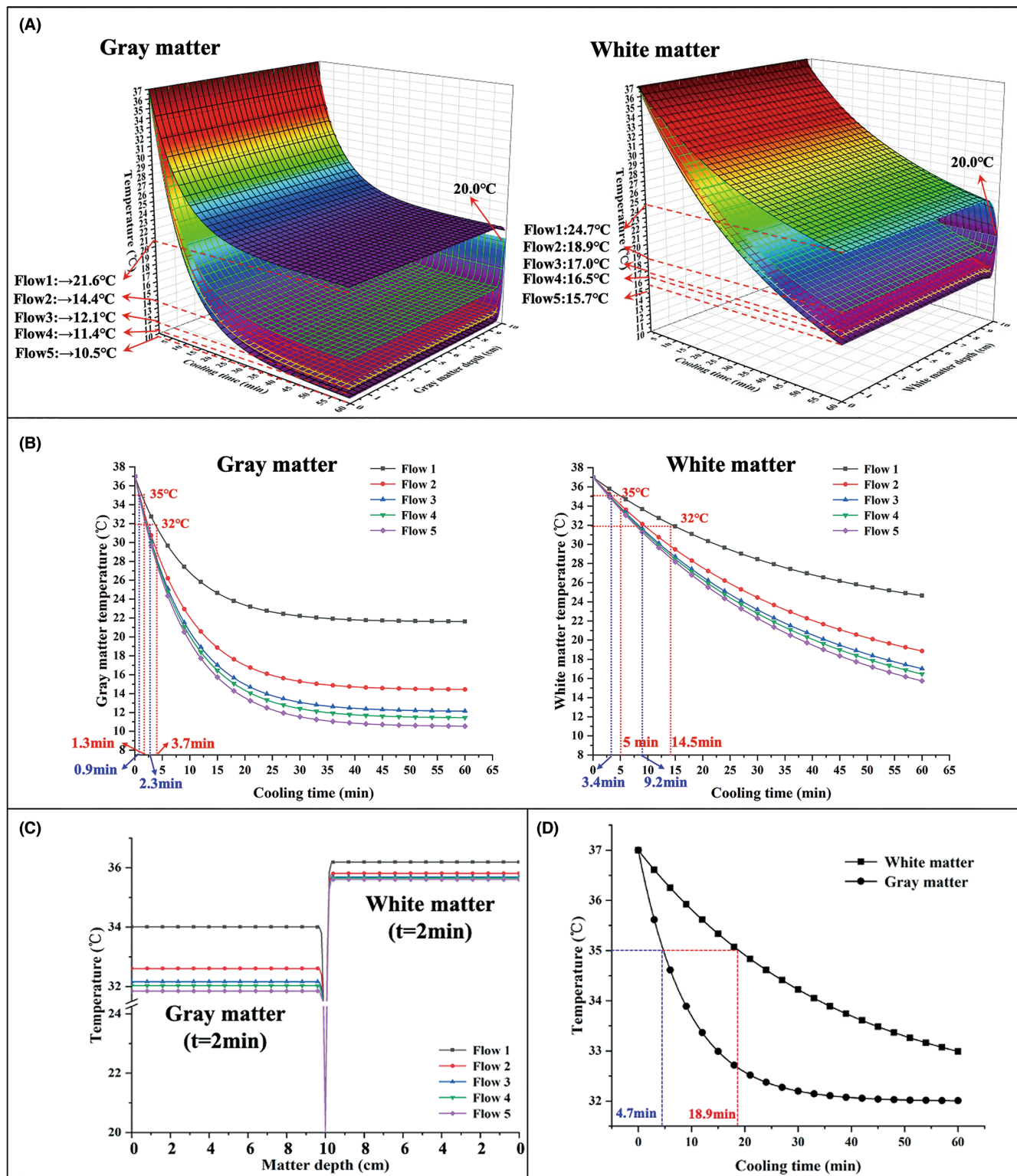
## 4 | DISCUSSION

We present the first experimental prototype instrument system which permits continuous intra-arterial autogenous blood perfusion

for safely and effectively selective cooling of AIS. To evaluate how the efficiency of the prototype system cooled brain tissue, this study used an in vitro simulation loop device and a computational numerical theoretical model to explore the effect of different flow rates in terms of times ( $t$ ) and depths ( $r$ ) on the brain tissue temperature during the IA-SCAI. The prototype instrument system could attain target brain tissue temperatures ranging from  $10.5$  to  $35^\circ\text{C}$  for a long duration by using varied infusion flows inside the in vitro simulation loop device, which was based on a 1:1 3D-printed physical cerebrovascular model using actual CT data. The development of an IA-SCAI prototype instrument system is critical to achieving clinical hypothermia transition. It serves as a research tool for determining the optimal parameters for autologous blood selective hypothermia and confirming the mechanism of neuroprotective effect for hypothermia. In this study, an in vitro experimental platform was fabricated based on the real human intracranial vascular system, which provides a convenient method to evaluate the feasibility and cooling efficiency of the IA-SCAI prototype instrument. Konostas demonstrated that the method including the in vitro study and a numerical theoretical model was an attempt to determine the feasibility of selective brain cooling with intracarotid saline infusion.<sup>20</sup> Our group also used this method to conduct a feasibility assessment on the intravascular interventional catheter<sup>36</sup> and heat exchanger<sup>37</sup> in the IA-SCAI prototype system.

### 4.1 | Comparisons with different hypothermic therapies

Currently, hypothermic therapy can be achieved using a variety of cooling methods and procedures, and there are the three most critical considerations: cooling targeting, cooling rate, and side effects (Table 2). Surface cooling is the common traditional hypothermic therapy. However, this approach was difficult to achieve targeted



**FIGURE 5** (A) Three-dimensional diagram representing the combined effect of cooling time and depth on temperature. (B) Effect of autologous blood infusion rates on the transient temperature of the gray and white matter of the brain. (C) Effect of autologous blood infusion rates on the steady-state temperature of the gray and white matter of the brain at 2 min. (D) Effect of autologous blood infusion rates on the transient temperature of the gray and white matter of the brain ( $T_{MCA} = 32^{\circ}\text{C}$ )

cooling on brain tissue with a poor cooling rate (only  $3.5^{\circ}\text{C}/\text{h}$ ).<sup>38</sup> Nasal cooling and intravascular non-perfusion device cooling as novel brain cooling have evolved into a viable and promising neuroprotective

hypothermic therapy but with an undesirable phenomenon of a drop ( $1.1\sim 3^{\circ}\text{C}$ )<sup>39,40</sup> in the core temperature to cause systemic hypothermia, which can lead to adverse effects outlined in Table 2. In 2002,

TABLE 2 The comparison of different hypothermic therapies

Hypothermic therapies	Companies and systems	Selective brain cooling	Cooling rate	Side effects
Surface cooling	<ul style="list-style-type: none"> <li>Emcools: Flexipad<sup>38</sup></li> <li>Natus Medical: Olympic cool-cap<sup>46</sup></li> <li>Cryothermic systems: Cooling pack</li> <li>C.R.Bard: Artic Sun<sup>38</sup></li> </ul>	No	2–6°C/h	Easy to cause systemic hypothermia <sup>8</sup> : shivering, infection, effects on drug clearance, hyperglycemia, electrolyte imbalance, effects on the cardiovascular system, changes in urine output, and effects on coagulation.
Nasal cooling	<ul style="list-style-type: none"> <li>Bene Chill: Rhino chill<sup>47</sup></li> </ul>	No	5.2±1.9°C/h <sup>47</sup>	Reduction in core temperature (1.1–2.2°C). <sup>39</sup>
Intravascular non-perfusion device cooling	<ul style="list-style-type: none"> <li>Pforzheim: Acandis<sup>40</sup></li> <li>Zoll: Thermoguard XP system<sup>38</sup></li> </ul>	Yes	1°C per 8.5 min <sup>40</sup>	Reduction in core temperature (~3°C). <sup>40</sup>
Intravascular perfusion saline cooling	<ul style="list-style-type: none"> <li>FocalCool: Seiratherm<sup>43</sup></li> </ul>	Yes	2.2±2.5°C/min <sup>43</sup>	Saline load increased the burden on the heart and reduce the hematocrit. <sup>43</sup>

TABLE 3 The time to target temperature and brain temperature between the in vivo and in vitro study

Subject	The in vivo study				The in vitro study			
	Infusion rate	Infusion duration	Time to target temp	Brain temp	Infusion rate	Infusion duration	Time to target temp	Brain temp
Rat	0.6 ml/min	10 min	<10 min	<35°C	0.6 ml/min	60 min	3.4 min	35°C
Monkey	5 ml/min	20 min	10 min	34°C	5 ml/min	60 min	14.8 min	34°C
Human <sup>a</sup>	10–30 ml/min	5–10 min	Not mentioned	35°C	10–30 ml/min	60 min	10.4 min	35°C

<sup>a</sup>The in vivo study was chosen from the following reference: rat,<sup>52</sup> monkey,<sup>53</sup> and human.<sup>14</sup>

TABLE 4 The cerebral blood flow ( $\omega_0$ ) and metabolic rate ( $q_0$ ) in rat, monkey, and human

Subject	Temp	Cerebral blood flow ( $\omega_0$ )	Ref.
Rat	38°C	108 ml/(min.100g)	Hagerdal et al. <sup>54</sup>
	37.5°C	113 ml/(min.100g)	Frietsch et al. <sup>55</sup>
	37.5°C	121 ml/(min.100g)	Kraff et al. <sup>56</sup>
Monkey	–	46.12 ml/(min.100g)	Daniel E et al. <sup>57</sup>
Human <sup>a</sup>	37°C	40 ml/(min.100g)	Stone et al. <sup>58</sup>
	37°C	25 ml/(min.100g)	Murkin et al. <sup>59</sup>
	37°C	33 ml/(min.100g)	Stephan et al. <sup>60</sup>
	37°C	34 ml/(min.100g)	Stephan et al. <sup>60</sup>
	38°C	50.6 ml/(min.100g)	Konstas et al. <sup>20</sup>
Subject	Metabolic heat production	Metabolic rate ( $q_0$ )	Ref.
Rat	1.99 W/400g	5124.25 W/m <sup>3</sup>	Refinetti et al. <sup>61</sup>
Monkey	7 W/kg	7210 W/m <sup>3</sup>	Adair et al. <sup>62</sup>
Human <sup>a</sup>	–	16,700 W/m <sup>3</sup>	Konstas et al. <sup>20</sup>

<sup>a</sup>The mass density was set as 1030 kg/m<sup>3</sup>.<sup>20</sup>

our group proposed intra-arterial selective cooling saline infusion as an SBC approach to achieve targeted cooling on brain tissue.<sup>41</sup> It has since been widely employed in rodent animal models,<sup>12,42</sup> large animal models,<sup>40,43,44</sup> and stroke patients<sup>14,15,45</sup> with the safety and feasibility. However, an excessive amount of saline perfusion into intracranial brain tissue might increase the strain on the heart, lower the hematocrit, and limit the duration of hypothermia for AIS patients.<sup>8</sup>

In 2009, our group devised the intra-arterial selective cooling autogenous blood infusion (IA-SCAI) in answer to the problem of prolonging ongoing treatments of selective brain hypothermia in AIS patients without the abovementioned negative effects.<sup>17</sup> In the study, the IA-SCAI prototype instrument system had a little change in the core temperature (–0.7–+0.2°C) through the in vitro experiment and ensured long-term hypothermia maintenance for 1 h.



TABLE 5 Summary of clinical studies on intra-arterial cold saline infusion

Authors	Subject	Infusion	Infusion rate	Infusion duration	Time to target temp	Brain temp	Core body temp
Choi et al., 2010 <sup>45</sup>	Non-stroke patients	Saline 4–17°C	33 ml/min	10 min	<10 min	–0.84°C	–0.15°C
Chen et al., 2016 <sup>14</sup>	AIS patients	Saline 4°C	10–30 ml/min	5–10 min	Not mentioned	–2°C	–0.1°C
Wu et al., 2018 <sup>15</sup>	AIS patients	Saline 4°C	10–30 ml/min	5–10 min	Not mentioned	Not mentioned	–0.5°C
This in vitro study	–	Simulated auto-blood 13.7°C	44.3 ± 0.2 ml/min	60 min	3.7 min (Gray matter)	–4.3°C	–0.2°C

## 4.2 | Mathematical models for estimation of brain temperature for in vivo data

### 4.2.1 | Pre-clinical experiments

For rodent models, some studies have concluded that selective brain cooling treatment immediately after ischemic stroke significantly improved neurobehavioral function. These findings are beneficial to unveil the underlining mechanisms involved in neuroprotection against acute cerebral ischemic injuries.<sup>48,49</sup> However, in some of the large animal and non-human primate studies, the reduction of infarct size and improved functional outcomes induced by selective brain cooling were not statistically different from their control groups, which may ascribe to the small sample size. Therefore, a larger number of subjects might be required to demonstrate the efficacy of this technique.<sup>50,51</sup>

The time to target temperature and the brain temperature from the in vivo and in vitro study is compared in Table 3. The calculation results from the numerical theoretical model in this manuscript were compatible with the brain temperature estimation of rat, monkey, and human during IA-SCAI. For the rat, the predicted values calculated by this model were not significantly different from those obtained in vivo, which can achieve rapid cooling (35°C) on brain temperature within 10 min. The numerical analysis of brain temperature obtained by the monkey, and the time to reach the target temperature was slower than that of in vivo experiments. For comparison with human data, the time to target temperature (35°C) in the numerical model was 10.4 min which was slower than in the in vivo study.

The baseline cerebral blood flow ( $\omega_0$ ) and metabolic rate ( $q_0$ ) were used for the calculation by the numerical theoretical model in this study (Table 4). The mean cerebral blood flow ( $\omega_0$ ) of rat, monkey, and human was 114 ml/(min.100g), 46.12 ml/(min.100g), and 36.56 ml/(min.100g), respectively. And, the metabolic rate ( $q_0$ ) was 5124.25 W/m<sup>3</sup>, 7210 W/m<sup>3</sup>, and 16,700 W/m<sup>3</sup>, respectively.

### 4.2.2 | Clinical data

Theoretically, controlled flow rates of autologous arterial blood to perfuse into the brain, the human body's blood circulation should be unaffected, which enable normal cerebral blood flow to be restored after the vessel recanalized, and the period of intravascular hypothermic perfusion could be lengthened significantly without hemodilution.

Therefore, in the mathematical model for IA-SCAI compared with IA-SCI saline perfusion, we were able to enhance the blood flow of autologous blood perfusion and improve the cooling capacity of IA-SCAI, allowing it to reach mild-to-moderate hypothermia faster and last longer time (within 5 minutes by >40 ml/min, as shown in Figure 5).

According to Konstas's model for brain temperature estimate of IA-SCI by saline (30 ml/min by 60 min), mild-to-moderate hypothermia was achieved within 10 minutes after the infusion, which was 18–42 times quicker than noninvasive whole-body cooling (3–7 hours) and 10–20 times faster than whole-body endovascular cooling (10–20 hours).<sup>63,64</sup> Despite the fact that IA-SCI saline perfusion could provide targeted brain tissue cooling without influencing the human body's core temperature, the burden on the heart and hematocrit limited its cooling duration.<sup>65</sup> The hematocrit was reduced by 31% and 25% after a 60-minute saline infusion at 30 and 50 ml/min. The mild-to-moderate hypothermia may be safely sustained for 90 minutes at a rate of 50 ml/min and 180 minutes at a rate of 30 ml/min.<sup>20</sup> In order to provide efficient neuroprotective effects, hypothermia treatment in AIS patients should be maintained for a long time, which meant that IA-SCI saline perfusion was not acceptable for longer time usage. And it's challenging to keep brain temperature below 35°C with lower saline infusion rates.<sup>66</sup>

As shown in Table 5, Choi et al.<sup>45</sup> selectively infused 33 ml/min cold saline (4–17°C) into 18 non-stroke patients for 10 min. The target brain temperature decreased by an average of 0.84°C whereas the core body temperature dropped by 0.15°C. The same studies of IA-SCI were also conducted by Chen<sup>14</sup> and Wu<sup>15</sup> through the infusion of 10–30 ml/min of 4°C saline on AIS patients. They also achieved a 2°C drop in brain temperature and maintained a core body temperature change between 0.1°C and 0.5°C. We circulated the simulated cold blood (13.7°C) with a higher infusion rate (44.3 ± 0.2 ml/min) for 60 min to achieve a lower brain temperature drop (–4.3°C). For comparison, the time to the target temperature in this study was similar to Chio's results (within 10 minutes) with little changes in core temperature. During the in vitro experiment, the brain temperature drop was bigger due to the use of a higher perfusion flow.

## 4.3 | Limitations and prospective of the study

Despite positive results in rodent and small mammal research, the neuroprotective effect of IA-SCAI on AIS patients has been still

debatable and cannot be widely used in clinical practice. The absence of rapid, precise, safe, and effective IA-SCAI hypothermia brain protection equipment, as well as the lack of accepted clinical pathway of hypothermia therapy for AIS patients, limits the clinical promotion of this technology. As a result, the IA-SCAI prototype system described in this study may be used as a research tool to solve these problems.

Next, we aim to construct a more realistic in vitro cerebrovascular and tissue simulation system based on the complex anatomy of the brain and continue to evaluate the effect of IA-SCAI in combination with Pennes' complete bio-thermal mathematical equation. To increase the safety of autologous blood perfusion by the IA-SCAI system for large animal models, the rolling blood pump described in this study should be replaced with a centrifugal blood pump in order to ensure long-term safe blood extracorporeal circulation as it has a lower hemolysis rate,<sup>67</sup> and the anticoagulant coating should be applied onto tubes and equipment.<sup>68</sup> In the future investigation, we will perform an in vivo study of IA-SCAI to evaluate the safety and efficacy of the prototype instrument system by using large AIS animal models. Our next step is to apply the prototype to the research of large animals to prepare for clinical validation, which needs to focus on the accurate temperature control of autologous blood cooling, the steady perfusion of intravascular autologous blood flow, and the preparation of AIS animal models.

## 5 | CONCLUSION

The prototype instrument system of IA-SCAI developed in this study offers a preliminary safety and efficacy assessment through the mathematical brain temperature estimation and the in vitro experiment. The experimental results showed that: (1) this prototype instrument system could safely cool simulated blood in vitro and return it to the target cerebral blood vessel. Different hyperthermia (mild, moderate, and severe) could be achieved by the system due to the adequate cooling capacity of the prototype, which could provide the lowest cooling temperature into the blood vessel of 10.5°C at 25 rpm (209.7 ± 0.8 ml/min). And, the core body temperature did not alter significantly (-0.7 ~ +0.2°C) after 1-h perfusion. (2) Using a mathematical model of biological heat transfer, the cooling rate and temperature distributions of the brain tissue were analyzed during the IA-SCAI, which showed a 2°C decrease within the initial 5 min infusion by 44 ml/min and 13.7°C perfusate. This system is a reliable tool for neuroprotective studies on stroke animal models. This technique can circumvent the adverse effects of saline perfusion and promote the clinical application of an autologous blood perfusion system for stroke therapy.

### CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

### DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. They are not publicly available due to ethical restriction.

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