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# Combined local hypothermia and recanalization therapy for acute ischemic stroke: Estimation of brain and systemic temperature using an energetic numerical model☆

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ABSTRACT

Local brain hypothermia is an attractive method for providing cerebral neuroprotection for ischemic stroke patients and at the same time reducing systemic side effects of cooling. In acute ischemic stroke patients with large vessel occlusion, combination with endovascular mechanical recanalization treatment could potentially allow for an alleviation of inflammatory and apoptotic pathways in the critical phase of reperfusion. The direct cooling of arterial blood by means of an intra-carotid heat exchange catheter compatible with recanalization systems is a novel promising approach. Focusing on the concept of "cold reperfusion", we developed an energetic model to calculate the rate of temperature decrease during intra-carotid cooling in case of physiological as well as decreased perfusion. Additionally, we discussed and considered the effect and biological significance of temperature decrease on resulting brain perfusion. Our model predicted a 2 °C brain temperature decrease in 8.3, 11.8 and 26.2 min at perfusion rates of 50, 30 and 10 $\frac{\text{ml}}{100\text{g} \cdot \text{min}}$, respectively. The systemic temperature decrease - caused by the venous blood return to the main circulation - was limited to 0.5 °C in 60 min. Our results underline the potential of catheter-assisted, intracarotid blood cooling to provide a fast and selective brain temperature decrease in the phase of vessel recanalization. This method can potentially allow for a tissue hypothermia during the restoration of the physiological flow and thus a "cold reperfusion" in the setting of mechanical recanalization.

## 1. Introduction

Two randomized clinical studies published in 2001 showed that mild therapeutic hypothermia (TH) in a range between 33 °C and 35 °C improves clinical neurological outcome in patients with cardiac arrest after return of spontaneous circulation (ROSC), followed by a recommendation in the therapy guidelines (Bernard et al., 2002; Holzer et al., 2002). Cerebral ischemia in acute stroke patients represents a considerably different pathophysiology than in cardiac arrest, since it emerges focally while other organs are physiologically perfused and it often persists for a longer time window of several hours. TH proved to be safe and feasible in acute stroke patients while its therapeutic efficacy still remains to be proven and is currently investigated in randomized clinical trials (van der Worp et al., 2014).

In a meta-analysis of animal stroke models with both temporary and permanent cerebral ischemia, hypothermia was correlated to an overall reduction of infarct core size of 44 % (Worp et al., 2007) at temperatures of 35 °C or below. Moreover, a neuroprotective effect was demonstrated for limited cooling times if local cooling by means of cold intra-carotid saline infusion was applied in a very early phase before or during reperfusion (Chen et al., 1992; Ehrlich et al., 2002; Holzer et al., 2005; Hwang et al., 2017). In this regard, TH may have the potential to favorably affect the biochemical pathways if applied early, i.e. before or during vessel recanalization.

Current cooling systems aim to induce systemic hypothermia by means of surface cooling or intra-venous catheters (Wu and Grotta, 2013). Both methods suffer from disadvantages for use in stroke patients in the setting of a vessel recanalization: 1) The rate of temperature reduction is limited by the thermal inertia of whole body, potentially missing the target temperature during the critical phase of

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**Abbreviations:**

| | |
|---|---|
| ACA | Anterior Cerebral Artery |
| CBF | Cranial Blood Flow |
| CCA | Common Carotid Artery |
| MCA | Middle Cerebral Artery |
| MT | Mechanical Thrombectomy |
| PCA | Posterior Cerebral Artery |
| ROSC | Return of Spontaneous Circulation |
| ROB | Rest of the Body |
| TH | Therapeutic Hypothermia |

reperfusion (van der Worp et al., 2014). *2*) The decrease of the body core temperature is potentially correlated with adverse effects such as cardiac arrhythmia, decreased cardiac output, shivering, disturbance of coagulation and an increased risk of infection such as pneumonia (Feigin et al., 2003; Labiche and Grotta, 2004).

The concept of local brain hypothermia aims at a faster induction of cerebral neuroprotection, avoiding the mentioned complications. Furthermore, the combination with endovascular recanalization techniques could potentially allow for an alleviation of inflammatory and apoptotic pathways in the critical phase of reperfusion. Several methods have been presented in the preclinical and clinical literature to selectively reduce the brain temperature to a lower value than core temperature, including helmets, neck cuffs and nasal spray (Chava et al., 2017; Song and Lyden, 2012). Direct cooling of arterial blood seems to be the most attractive therapeutic strategy in terms of cooling rate due to the role of blood as most effective energy vector in deep tissues. A recently published study involving 113 acute ischemic stroke patients with cerebral large vessel occlusion demonstrated the safety of a short-duration (15 min) intra-arterial infusion of cold saline at 4 °C in combination with standard endovascular mechanical thrombectomy vs. standard therapy alone (Wu et al., 2018). Moreover, the investigators found a trend towards clinical benefit in the group of patients receiving combined therapy with selective cold saline infusion. However, capacity and duration of direct intra-arterial saline infusion may be limited by volume overload and hemodilution effects (Esposito et al., 2014). Alternatively, a new endovascular catheter system for local intra-carotid blood cooling by means of a cold saline closed loop was recently presented (Cattaneo et al., 2015a). The compatibility with catheters for aspiration and mechanical thrombectomy (MT) aims at rapid induction of TH in the ischemic penumbra using the cooling effect of cranial blood flow (CBF) via collaterals before and during the recanalization procedure. The combined system is conceived to enable a “cold reperfusion” of the ischemic core during and after MT treatment (van der Worp et al., 2010). Moreover, compared to injection of cold saline, the system shall allow for a longer hypothermia procedure without concerns regarding hypervolemia or hematocrit reduction.

In this work, we developed an energetic model to calculate the performance of the new cooling catheter, addressing the following questions:

- Can a potentially neuroprotective temperature of 35 °C or lower be reached within the ischemic penumbral tissue before the occluded cerebral artery is recanalized by MT treatment and reperfusion occurs?
- How does the temperature decrease depend on cerebral perfusion rate in the penumbra?
- How does the cerebral temperature decrease affect resulting brain perfusion and physiological regulation?
- How does local hypothermia affect systemic temperature due to venous blood return from the brain?

The first two questions address a pragmatic issue in the clinical setting: the time interval between the positioning of the cooling catheter within the internal carotid artery and the actual recanalization of the occluded brain artery may be rather short in modern MT procedures, ranging between 5 min and 30 min or also more e.g. in case of challenging extra- and intra-cranial vasculature, large clot loads, or sticky fibrin-rich clots, which maybe harder to retrieve. In this time window, the brain should have reached a lower temperature for a cold reperfusion in a neuroprotective range. The third question concerns the body’s behavior due to hypothermia and biological regulation mechanisms. The fourth question relates to a safety aspect, which is claimed as an advantage of local cooling compared to systemic cooling.

## 2. Material and methods

### 2.1. Energetic model

#### 2.1.1. Model compartments

For the assessment of the decrease in temperature due to cold brain perfusion, three compartments were defined. The first and second compartment reflect the perfusion areas of the anterior and middle cerebral artery (ACA, MCA) as the brain regions receiving cold blood from the common carotid artery (CCA) where the cooling catheter is placed. Only ipsilateral collateralization is assumed, leading to a perfusion at the same low temperature in the whole penumbra region since all side branches of the carotid artery are fed by cooled blood. Assuming a total brain volume $V_{\mathrm{Brain}}$ of 1355 $\mathrm{cm}^3$ (Allen et al., 2002), the volumes of the right ACA and right MCA perfusion areas were calculated using data of Mut et al. (2014), who evaluated magnetic resonance angiography datasets to reconstruct the cerebral artery network ($V_{\mathrm{ACA,right}} = 153.85\ \mathrm{cm}^3$, $V_{\mathrm{MCA,right}} = 291.21\ \mathrm{cm}^3$).

The third compartment reflects all other body regions, which are not directly perfused by the cold blood, including the contralateral side of the brain and the rest of the body (RoB). The compartments build a closed loop system, with blood from the hypothermic compartments mixing with the blood of the systemic body. The structure of the temperature model is depicted in Fig. 1.

### 2.2. Numerical energetic temperature calculation

Pennes’ bio-heat-equation can be used to calculate the spatial and temporal course of the temperature T in living tissue. The equation considers heat conduction in tissue, heat generation by metabolism and heat exchange between arterial blood and tissue (Pennes, 1998):

$$\rho_T c_{\mathrm{T}} \frac{\partial T}{\partial t} = \nabla(\lambda_{\mathrm{T}} \nabla T) - c_{\mathrm{Bl}} W_{\mathrm{Bl}} (T - T_{\mathrm{a}}) + P_{\mathrm{Met}} \quad (1)$$

where $\rho_T$ is the tissue density ($\frac{\mathrm{kg}}{\mathrm{m}^3}$), $c_{\mathrm{T}}$ the specific heat ($\frac{\mathrm{J}}{\mathrm{kg \cdot K}}$), $\lambda_{\mathrm{T}}$ the thermal conductivity ($\frac{\mathrm{W}}{\mathrm{K \cdot m}}$), $c_{\mathrm{Bl}}$ the specific heat of blood ($\frac{\mathrm{J}}{\mathrm{kg \cdot K}}$), $W_{\mathrm{Bl}}$ the volumetric perfusion rate of the tissue ($\frac{\mathrm{kg}}{\mathrm{m}^3 \cdot \mathrm{s}}$), $T_{\mathrm{a}}$ the blood temperature of the perfusing artery (K) and $P_{\mathrm{Met}}$ the metabolic heat of the tissue ($\frac{\mathrm{W}}{\mathrm{m}^3}$). However, this partial differential equation needs extensive parameterization and entails many uncertainties. In this work, we focused on the temperature change due to the hypothermic treatment, which is related to the artificial blood cooling. We neglected the additive effect of metabolism and heat exchange with the environment, considering them to be unaffected by the moderate brain cooling. Thus, we simplified the bio-heat equation and only considered the effect of heat exchange induced by perfusion. In this context, a uniform spatial heat distribution is assumed. Eq. (1) was simplified and the temperatures in the hypothermic compartments $T_{\mathrm{ACA}}$, $T_{\mathrm{MCA}}$ were calculated as follows:

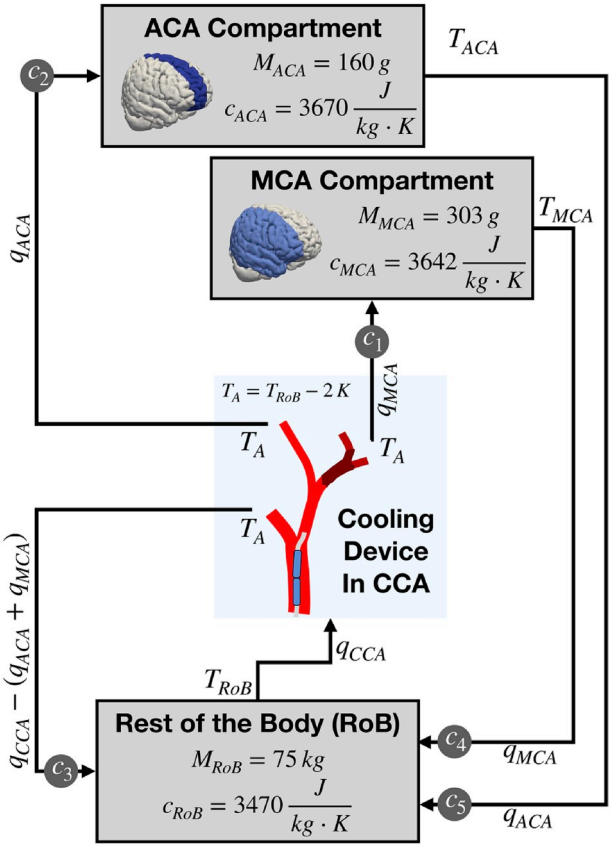


**Fig. 1.** Schematic of the energetic temperature model and its three compartments. The coefficients $c_1$-$c_5$ were used for the temperature calculation in the respective compartments and consist of blood and tissue properties.

$$\frac{dT_{MCA}}{dt} = -\frac{c_{Bl}\cdot\rho_{Bl}\cdot q_{MCA}}{M_{MCA}\cdot c_{MCA}}(T_{MCA} - T_A) = -c_1\cdot(T_{MCA} - T_A) \quad (2)$$

$$\frac{dT_{ACA}}{dt} = -\frac{c_{Bl}\cdot\rho_{Bl}\cdot q_{ACA}}{M_{ACA}\cdot c_{ACA}}(T_{ACA} - T_A) = -c_2\cdot(T_{ACA} - T_A) \quad (3)$$

with $\rho_{Bl}$ being the blood density ($\frac{kg}{ml}$), $T_A$ the arterial blood temperature (°C) and $q_{ACA}$, $q_{MCA}$ represent the respective blood flow rates ($\frac{ml}{s}$). $M_{ACA}$ is the mass of the perfused brain tissue (kg) by the ACA and was calculated under consideration of the composition of white and gray matter (Mut et al., 2014) and the respective densities (Hasgall, 2018). $M_{MCA}$ is the mass of the perfused brain tissue by the MCA and was calculated in the same way, but taking into account different ischemic degrees.

The same assumption as for spatial temperature distribution (Eq. (2) and (3)) is made for the energetic heat transfer between the hypothermic compartments and the rest of the body $T_{RoB}$:

$$\frac{dT_{RoB}}{dt} = -c_3\cdot(T_{RoB} - T_A) - c_4\cdot(T_{RoB} - T_{MCA}) - c_5\cdot(T_{RoB} - T_{ACA}) \quad (4)$$

with $c_3 = \frac{c_{Bl}\rho_{Bl}(q_{CCA} - (q_{ACA} + q_{MCA}))}{M_{RoB}c_{RoB}}$ and $c_4 = \frac{c_{Bl}\rho_{Bl}q_{MCA}}{M_{RoB}c_{RoB}}$ and $c_5 = \frac{c_{Bl}\rho_{Bl}q_{ACA}}{M_{RoB}c_{RoB}}$, where $M_{RoB}$ is the mass (kg) and $c_{RoB}$ the specific heat ($\frac{J}{kg\cdot K}$) of the rest of the body. $q_{CCA}$ is the arterial blood flow rate in the CCA, which was determined using a 1D model of cerebral hemodynamics (Lutz et al., 2019). To obtain a closed-loop temperature system (cf. Fig. 1), we used the calculated temperature $T_{RoB}$ as blood temperature in the CCA in front of the cooling catheter. Under the assumption of constant cooling by the cooling catheter, the perfusing arterial blood temperature $T_A$ is given by:

$$T_A(t) = T_{RoB}(t) - \Delta T_{Cooling} \quad (5)$$

**Table 1**
Parameters used for the temperature calculation.

| Parameter | Value | Source |
|---|---|---|
| Density blood: $\rho_{Bl}$ | $1049.8\,\frac{kg}{m^3}$ | Hasgall (2018) |
| Density GM: $\rho_{GM}$ | $1044.5\,\frac{kg}{m^3}$ | Hasgall (2018) |
| Density WM: $\rho_{WM}$ | $1041.0\,\frac{kg}{m^3}$ | Hasgall (2018) |
| Heat capacity blood: $c_{Bl}$ | $3617.0\,\frac{J}{kg\,K}$ | Hasgall (2018) |
| Heat capacity RoB: $c_{RoB}$ | $3470.0\,\frac{J}{kg\cdot K}$ | Hasgall (2018) |
| Heat capacity GM: $c_{GM}$ | $3695.8\,\frac{J}{kg\cdot K}$ | Hasgall (2018) |
| Heat capacity WM: $c_{WM}$ | $3582.8\,\frac{J}{kg\cdot K}$ | Hasgall (2018) |
| Mass RoB: $M_{RoB}$ | 75 kg | |
| Blood flow CCA: | $308.4\,\frac{ml}{min}$ | Lutz et al. (2019) |

with $\Delta T_{Cooling}$ being a fixed temperature decrease, reflecting the performance of the cooling catheter device. Table 1 shows an overview of all fixed parameters and their values for the temperature calculation.

All model equations were implemented into MATLAB (R2018b, The MathWorks, Nattick, MA, USA) for numerical simulation.

### 2.2.1. Effect of cooling on flow

Konstas et al. (2007) performed an extensive literature research investigating the effect of TH on CBF. Analyzing the pooled data from animal and human studies, they assumed that under physiological conditions CBF shows an exponential decrease with brain temperature as long as the brain temperature stays above 25 °C. Therefore, they derived the following equation:

$$q_{Bl}(T) = q_{Bl,37}\cdot 2.961^{0.08401(T - 37\,°C)} \quad (6)$$

where $q_{Bl,37}$ is the baseline blood flow for 37 °C.

However, since this equation can be assumed to be valid only for physiologically perfused tissue, we expanded Konstas' equation for the MCA compartment and included an additional weighting factor $(1 - \frac{q_{MCA,37}}{q_{MCA,ref,37}})$ for ischemic perfusion rates. Including this additional factor leads to a milder decrease in MCA perfusion depending on the ischemic degree of the brain tissue:

$$q_{MCA}(T_{MCA}) = q_{MCA,37}\left(1 - \frac{q_{MCA,37}}{q_{MCA,\ ref,37}}\right)\left(1 - 2.961^{0.08401(T_{MCA} - 37\,°C)}\right) \quad (7)$$

Here $q_{MCA,ref,37}$ is the physiological, reference blood flow rate in the MCA for 37 °C under non-ischemic conditions.

### 2.2.2. Balloon cooling catheter system

The analyzed intracarotid balloon cooling catheter system (Acandis, Pforzheim, Germany) is built of four serially arranged, non-compliant balloons (diameter of 4 mm and length of 20 mm, respectively) at the catheter tip, which are perfused with coolant (0.9 % sodium chloride). The coolant is circulated by an external roller pump through a closed-loop inner-catheter cooling circuit consisting of two lumens, which lead the coolant into and out of the balloons, without direct blood contact. An external thermostat provides a constant coolant temperature of approximately 6 °C. A third lumen allows passage of a 2.5 F microcatheter and thus distal access for MT (Cattaneo et al., 2016a, 2015b). In vitro experiments of the described cooling catheter using an artificial blood circuit with flow rates of 250 and $400\frac{ml}{min}$ revealed a mean temperature drop between catheter inlet and outlet of $-2.17 \pm 0.07$ °C and $-1.55 \pm 0.06$ °C respectively (Cattaneo et al., 2015b). For our calculations, we supposed a temperature decrease $\Delta T_{Cooling} = -2.0$ °C. This means, that the "cold blood" is 2.0 °C colder than the rest of the body at each time point of the calculation.

*2.2.3. Perfusion variation in the MCA compartment*

After middle cerebral artery occlusion, the perfusion of the brain tissue in the penumbra region is decreased distinctly and depends on the extent of the patient's collateralization (Leng et al., 2016; Liebeskind, 2003; Pham and Bendszus, 2016). Different values can be found in literature for perfusion rates of brain tissue for physiological and ischemic states. Following an overview of cerebral perfusion rates by Baron et al., we assumed 50 $\frac{ml}{100\,g\cdot min}$ as physiological perfusion. To address the impact of typical perfusion rates in ischemic core and the penumbra, we assumed 10 and 30 $\frac{ml}{100\,g\cdot min}$, respectively (Baron, 2001).

Since successful recanalization leads to an increasing perfusion in the ischemic tissue and especially in the penumbra, a change in perfusion was also modeled. For this purpose, the perfusion was raised from 10 to 50 $\frac{ml}{100\,g\cdot min}$ after 10 or 30 min of cooling. This approach allowed to also evaluate the impact of the time of recanalization on resulting brain temperatures.

## 3. Results

### 3.1. Constant perfusion

Independent of the chosen perfusion rate, the temperature decrease of the hypothermic compartments were the strongest in the first 10–20 min of cooling and showed an exponential course (cf. Fig. 2, left). Subsequently, the decrease weakened and became more linear, following the course of the rest of the body (cf. Fig. 2, right). The total cooling effect was most pronounced for physiological perfusion (50 $\frac{ml}{100\,g\cdot min}$): The temperature in the MCA compartment decreased by 1.0 °C in 1.5 min and 2.0 °C in 8.3 min ($T_{HTC,0} = 37$ °C). In comparison, the systemic temperature dropped considerably slower. At the time of a 2 °C temperature decrease in the MCA compartment, the systematic temperature decrease was 0.07 °C.

In the case of perfusion reduction, the time to reach a decrease of 1.0 and 2.0 °C in temperature increased to 2.3 min and 11.8 min for 30 $\frac{ml}{100g\cdot min}$ and to 6.7 min and 26.2 min for 10 $\frac{ml}{100g\cdot min}$, respectively. After 60 min of cooling, the temperature decrease in the MCA compartment was similar for all perfusion rates, ranging from 2.5 °C for 50 $\frac{ml}{100g\cdot min}$ to 2.4 °C for 10 $\frac{ml}{100g\cdot min}$. Due to the identical perfusion rates, the temperature in the ACA compartment followed the temperature in the MCA compartment for physiological perfusion. As mentioned above, the predicted temperature decreases for the rest of the body were considerably lower compared to the hypothermic compartments. After 1 h of cooling, the systemic temperature decreased by 0.52 °C for all analyzed MCA perfusion rates (Fig. 2, right).

The maximum temperature-induced decrease in MCA perfusion rate was 20.4 %, reached for physiological perfusion after 1 h of cooling (cf. Fig. 3). Table 2 shows the resulting decreases of $T_{HTC}$, $T_{RoB}$ and $q_{Bl}$ after 10, 30 and 60 min of cooling for all three perfusion rates.

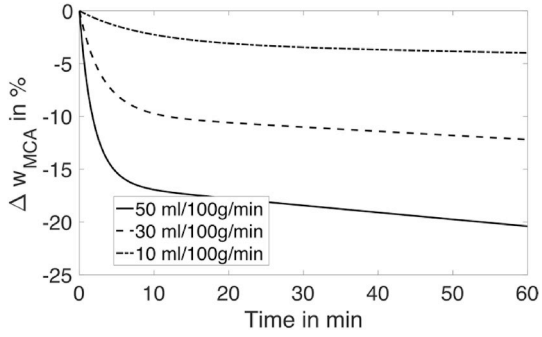


**Fig. 3.** Course of change in MCA perfusion for different constant MCA perfusion rates.

**Table 2**
Resulting decreases in temperature and MCA blood flow.

| Cooling time | Parameter | Perfusion in $\frac{ml}{100\,g\cdot min}$ | 10 | 30 | 50 |
|---|---|---|---|---|---|
| 10 min | $\Delta T_{MCA}$ (°C) | | 1.31 | 1.94 | 2.04 |
| | $\Delta T_{RoB}$ (°C) | | 0.08 | 0.08 | 0.08 |
| | $\Delta q_{MCA}$ (%) | | 2.26 | 9.73 | 16.94 |
| 30 min | $\Delta T_{MCA}$ (°C) | | 2.08 | 2.22 | 2.24 |
| | $\Delta T_{RoB}$ (°C) | | 0.26 | 0.26 | 0.26 |
| | $\Delta q_{MCA}$ (%) | | 3.45 | 11.01 | 18.43 |
| 60 min | $\Delta T_{MCA}$ (°C) | | 2.43 | 2.49 | 2.50 |
| | $\Delta T_{RoB}$ (°C) | | 0.52 | 0.52 | 0.52 |
| | $\Delta q_{MCA}$ (%) | | 3.98 | 12.19 | 20.40 |

### 3.2. Perfusion increase (simulated recanalization)

We chose different points in time for an increase in MCA perfusion from 10 to 50 $\frac{ml}{100g\cdot min}$, mimicking recanalization after MT, and calculated the effect on temperature course. A 2.0 °C decrease in temperature of the MCA compartment was reached within 14.5 min after start of brain cooling if the simulated recanalization was realized 10 min after start of cooling, while 26 min were needed if the recanalization was simulated after 30 min of cooling. The maximal temperature difference in the hypothermic compartment for the different time points of recanalization was 0.4 °C (c.f. Fig. 4).

## 4. Discussion

Our energetic temperature model predicts a profound temperature decrease in the hypothermic compartments within the first 5-10 min for selective endovascular intra-carotid blood cooling. Depending on the MCA perfusion, the reached temperatures in this time window ranged between 35 and 35.5 °C. For a moderately decreased ischemic perfusion rate (30 $\frac{ml}{100g\cdot min}$) the resulting temperatures in the MCA compartment

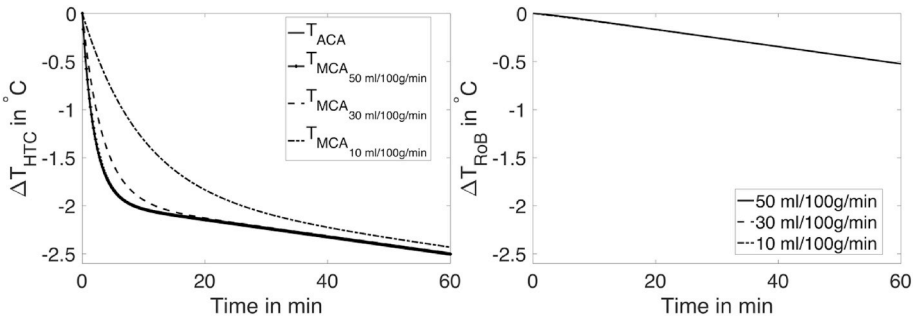


**Fig. 2.** Course of temperature change for different constant MCA perfusion rates. Left: Temperature change in the hypothermic compartments (ACA and MCA perfusion areas). Right: Temperature change in the rest of the body.

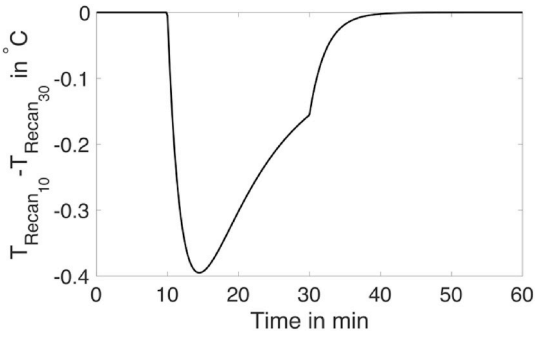


**Fig. 4.** Resulting difference in temperature of the MCA compartment for a complete vessel recanalization performed after 10 or 30 min from the cooling start.

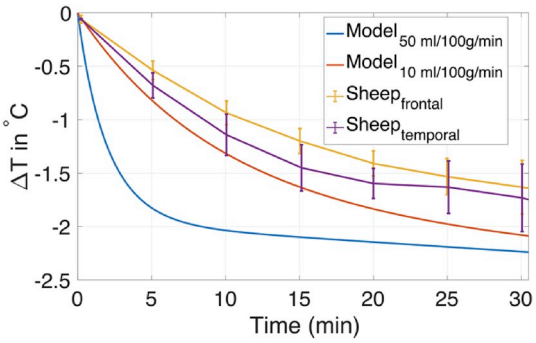


**Fig. 5.** Comparison of the model predicted cerebral temperature decrease to results of an animal study in nine sheep (Cattaneo et al., 2016b).

were in a similar range compared to physiological MCA perfusion (50 $\frac{ml}{100g \cdot min}$), while for low perfusion of 10 $\frac{ml}{100g \cdot min}$, time to reach a 2.0 °C decrease was markedly longer.

### 4.1. Comparison of the results

#### 4.1.1. Comparison with computational temperature models

In 2004, Slotboom et al. simulated the effect of locally induced hypothermia for treatment of acute ischemic stroke using a simple cerebral temperature model (Slotboom et al., 2004). In their model, they analyzed different cold saline infusion rates of an intra-arterial micro-catheter (7.5, 15, 30, 45 $\frac{ml}{min}$) and assumed a constant outlet coolant temperature of 15 °C. Their model predicted a mild-to-moderate (34 − 28 °C) hypothermia for 300 g infarcted brain tissue within 6 min depending on the infusion rate. The effect on systemic body temperature – considering the amount of extracted energy from the body by cooling – was also evaluated. For 1 h of cooling, a low outlet coolant temperature of 2 °C, and a high infusion rate of 1200 $\frac{ml}{min}$, they predicted a maximum decrease in systemic temperature of 0.7 °C. Our results are in accordance with Slotbooms' findings, since the large part of temperature decrease occurred in the first 15 min of intracarotid cooling and a moderate effect of local TH on systemic temperature was shown. The predicted stronger cooling effect of their model can be explained by the different cooling method analyzed, which allows much higher heat exchange in the first cooling phase by applying high volumes of cold saline. Furthermore, in contrast to our model, they did not consider systemic temperature coupling and did not take temperature dependent flow regulation into account. A comparison between the results of Slotboom's and our model for ischemic flow conditions, is not possible since they only considered coolant flow behind the occluding blood clot.

In 2006, Konstas et al. used a hemispherical, three-dimensional numerical model to examine the transient and steady-state temperature response to selective brain cooling by cold saline infusion in the internal carotid artery (Konstas et al., 2007). In their model, they distinguished between healthy brain and brain with ischemic stroke (non-infarcted tissue, penumbra, ischemic core). The model predicted a mean temperature in the ischemic penumbra of 35.83 °C after 60 min of cold saline infusion (infusion rate: 10 $\frac{ml}{min}$, outlet temperature: 12.1 °C). In contrast to our model, Konstas et al. analyzed inducement of local TH by cold saline infusion via an intra-carotid catheter using a simple, hemispherical three-dimensional brain geometry. In their model, they distinguished spatially different brain tissue classes, but did not consider systemic temperature coupling nor the effects of ischemic blood flow conditions.

#### 4.1.2. Comparison with animal feasibility studies

In recent animal experiments with 9 sheep, the cooling performance of the novel cooling catheter system described above was analyzed (Cattaneo et al., 2016b). For this purpose, temperature probes were placed in the animals' frontal and temporal brain cortices bilaterally by neurosurgical burr-hole craniotomies. The cooling catheter system was located in the common carotid artery and cortical brain, nasal, and systemic (inferior vena cava) temperatures were measured. The detailed setup and the precise study protocol were described previously (Cattaneo et al., 2016b).

The comparison between the measured in-vivo animal data and our numerical model is shown in Fig. 5. A similar temperature curve can be observed between in-vivo results and the numerical simulation at 10 $\frac{ml}{100\,g \cdot min}$. The milder temperature decrease measured in the first 20 min can be explained by the different common carotid artery blood flow velocities in the non-ischemic sheep and our assumed values (254 − 308 $\frac{ml}{min}$). Carotid blood flow rates have great impact on the cooling performance of the cooling catheter. In in-vitro experiments with an artificial blood circuit, Cattaneo et al. measured a resulting mean temperature gradient induced by the cooling catheter system of 2.17 ± 0.07 °C and 1.55 ± 0.06 °C at flow rates of 250 and 400 $\frac{ml}{min}$, respectively (Cattaneo et al., 2015a). Sonography in the animal study showed a diameter in the midsegment of the common carotid artery of 6.3 ± 0.6 mm and a blood flow velocity of 51.9 ± 18.7 $\frac{cm}{s}$, leading to a minimum calculated flow of 508.3 $\frac{ml}{min}$ and thus to a lower temperature drop behind the catheter.

### 4.2. Limitations

#### 4.2.1. Shortcomings of the energetic view

For our calculation of the brain temperature, we adapted Pennes' original bio-heat equation, which showed remarkable success in various applications and was used several times for simulation of hypothermia (Jiji, 2009).

Although there are several more complex and detailed equations or extensions for bio heat transfer –Pennes' equation does not account for directional blood perfusion, vascular architecture and the actual thermal equilibration site– (Chen and Holmes, 1980; Sparrow et al., 2018; Weinbaum et al., 1984; Weinbaum and Jiji, 1985), Pennes' original bio-heat-equation results in realistic and reliable temperatures (Schwarz, 2009) and is still basis for bio-heat modelling (Jiji, 2009).

In our energetic model, we focused on a fast estimation of time dependent changes in intracranial and systemic temperature. Since we were only interested in the macroscopic temperature decrease and not in the exact spatial temperature profile, we assumed a uniform heat distribution in space (negligible conductive heat transport). However, the model does not take the effect of warm blood mixing flow via leptomeningeal collaterals from contralateral internal carotid artery as well as from the posterior cerebral artery via the vertebrobasilar circulation into account, which might overestimate the overall cooling performance.

#### 4.2.2. Consideration of metabolism

Neglecting of the metabolic heat generation - as we did - seems to be valid for the ischemic core (Konstas et al., 2007). Generally, the thermoregulation in the human body keeps the internal body temperature nearly constant over a wide range regardless of external influences, using heat-transfer to the environment variably composed of radiation, conduction, convection and evaporation. Under physiological conditions, the heat dissipation is in balance with the metabolic heat generation of the body and leads to homoeothermic steady-state conditions. In our model, no spatial differentiation of tissue is considered and a balance of heat dissipation and metabolic heat generation was assumed for penumbra as well as for physiologically perfused tissue. Also, we did not consider the impact of inflammatory process in the penumbra on temperature as well as the effect of temperature gradient with the environment.

#### 4.2.3. Blood flow

Under physiological conditions, CBF is well regulated and provides a constant, stable perfusion of brain tissue. However, the effect of selective TH in combination with ischemia on CBF is mainly unknown and different hypotheses exist in literature. For our model, we adapted the approach of Konstas et al. (2007). They pooled data from studies investigating the effect of hypothermia on CBF and derived an analytic expression of the effect of TH on CBF during intra-cranial cold saline infusion (compare Sec. 2.1). Nevertheless, blood flow regulation in the brain is a complex control circuit and there are also hypotheses supposing an increase in CBF caused by hypothermia. For example, Mustafa et al. observed a cooling-induced carotid artery dilatation in an experimental study with isolated vessels of New Zealand white rabbits (Mustafa and Thulesius, 2002). According to their results, they assumed that, an increase in CBF might lead to the observed positive effect of selective TH for ischemic stroke in animal studies. Zhu et al. and Sukstanskii et al. described a so-called shielding effect of the brain tissue against temperature change from external cooling sources (Sukstanskii and Yablonskiy, 2007, 2006; Zhu et al., 2006). They considered a temperature decrease to cause an increasing CBF restoring physiological thermal conditions using the perfusion with “warm” systemic blood for compensation. Nevertheless, considering the fact that Konstas et al. used animal and human studies and evaluated far more data, we decided to incorporate a declining CBF for TH in our model.

In our model, we assumed a constant blood flow in the ACA and CCA, independent of the perfusion rate in the perfusion area of the MCA. In reality, the blood flow will adapt to the flow conditions in the MCA. However, a detailed blood flow model would be required to take this fact into account.

#### 4.2.4. Outlook

As next steps, we aim at evaluating the effects of selective endovascular intra-carotid blood cooling combining the complex anatomy of the human head with Pennes’ full bio heat equation. The temperature model will be coupled with a detailed model of hemodynamics and different patterns of collateral perfusion to evaluate the use of selective TH as treatment for acute ischemic stroke due to MCA occlusion.

## 5. Conclusion

Our results demonstrate a decrease in temperature of perfused brain tissue in the range of $1.5 - 2\ ^{\circ}C$ within the first 15 min after start of cooling even for reduced MCA perfusion rates. This underlines a potential positive impact of selective induced TH on brain regions suffering from reduced blood perfusion during stroke, especially in the penumbra. The regulation of cerebral perfusion and temperature has considerable biological significance. However, underlying mechanisms still remain unknown and there are controversial hypotheses. In our model, we considered a decrease in cerebral blood flow due to the intracarotid blood cooling, which led to a maximum of 20 % reduction in MCA flow.

Our results suggest that “cold reperfusion” and effective cooling of penumbral tissue has a potential within the time window of MT. Furthermore, the predicted mild systemic cooling reflects a lower risk for side effects compared to current systemic cooling systems for TH.

## Author disclosure statement

YL, OD, GC made a substantial contribution to the study concept and developed the numerical model.

YL conducted the simulations and wrote the manuscript.

GC and SM contributed in writing the manuscript and provided data.

AL, OD, GC, SM provided technical expertise and revised the article critically for important intellectual content. All authors approved the final version of the manuscript.

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*in press

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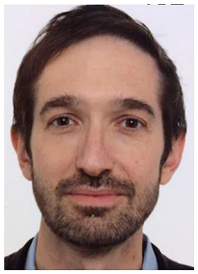

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