Review Article

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DOI: 10.4103/bc.bc_54_19

Review of selective brain hypothermia in acute ischemic stroke therapy using an intracarotid, closed-loop cooling catheter

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Abstract:

In acute ischemic stroke patients, selective brain hypothermia is a promising concept aiming at a fast decrease of brain temperature and thus neuroprotection in the acute phase of ischemia. At the same time, the emergence of mechanical thrombectomy (MT) as an effective treatment in large-vessel occlusion opens the door for a combination of neuroprotective approaches in the frame of a neurovascular, catheter-based intervention. In this regard, intracarotid cooling is a very effective energetic approach, using the blood supply to the penumbra as a fast transport vector for heat exchange in affected brain regions. We review the state of development of a novel closed-loop cooling catheter, describing design-related as well as procedural aspects and presenting results from different theoretical and experimental studies. Finally, we compare the concept with two alternative methods: cold saline infusion and extracorporeal blood cooling. We focus on the combination with MT, considering the effect of different and variable perfusion rates on the final goal of a "cold reperfusion" at the time of blood flow restoration.

Keywords:

Hypothermia, neuroprotection, mechanical thrombectomy, stroke

Introduction

Therapeutic hypothermia has been suggested to be a potential therapeutic approach offering a viable neuroprotective strategy for patients with acute ischemic stroke (AIS).[1] Moreover, selective brain hypothermia (SBH) is a promising therapeutic concept to provide a fast brain cooling while keeping the body temperature at a higher temperature level.[2] The main goal of this approach is a faster achievement of target temperature in the brain parenchyma compared to systemic cooling techniques since heat exchange is confined to the brain mass and a lower energy amount is needed. In addition, potential deleterious systemic side effects of cooling such as pneumonia, shivering, venous thrombosis, and hypotension are potentially avoided or at least limited.

The concept of fast and locally confined SBH has the potential to provide a rapid, early, and thus highly efficacious neuroprotective effect in AIS patients, where underperfused penumbra progressively turns into unsalvageable infarct within few hours after stroke onset. Moreover, in the case of AIS due to a large-vessel occlusion (LVO), endovascular mechanical thrombectomy (MT) has proved to be an extremely beneficial therapy with high rates of successful revascularization of LVO with a low number needed to treat. However, according to the meta-analysis of recent randomized controlled clinical trials, only 46% of patients treated with MT achieved a

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Submission: 22-11-2019
Revised: 25-11-2019
Accepted: 05-12-2019

How to cite this article: Cattaneo G, Meckel S. Review of selective brain hypothermia in acute ischemic stroke therapy using an intracarotid, closed-loop cooling catheter. Brain Circ 2019;5:211-7.

favorable clinical outcome with functional independence at 90 days posttreatment.[3] Therefore, many therapeutic endovascular approaches that combine MT with other agents or techniques for providing neuroprotection in LVO stroke patients are currently being investigated. SBH using the same endovascular access as for the MT procedure appears particularly promising among many others as it may be applied during the critical phase of reperfusion, which can potentially activate inflammatory pathways resulting in a reperfusion injury.[4,5]

Among possible techniques for SBH in AIS patients, including helmets and intranasal sprays, direct blood cooling in the large brain-supplying arteries such as the carotid artery has the advantage to use the blood flow as a strong energy vector flowing directly in the brain parenchyma, avoiding significant heat dissipation in surrounding tissues as in surface or intravenous cooling. Moreover, direct blood cooling can be combined with MT in the scope of one endovascular procedure, using the same access and navigation instruments and thus simplifying the procedure. Three different methods have been suggested to directly cool the arterial blood supplying the brain, potentially in the frame of a catheter-based intervention for MT based on (1) extracorporeal blood cooling, (2) cold saline infusion, and (3) intracarotid closed-loop cooling.

In this work, we present a review of the intracarotid cooling, pointing out on the preclinical evaluation of a new balloon catheter system including numerical, *in vitro*, and *in vivo* investigation. Furthermore, we discuss this cooling method in relation to the alternative techniques mentioned above in view of a potential clinical application.

Concept of Intracarotid, Closed-Loop Catheter

In Figure 1, brain cooling by means of the intracarotid catheter developed by Acandis GmbH, Germany, is schematically depicted. The catheter consists of a 3-luminal central shaft with an outer diameter of around 3.3 mm corresponding to an 8-Fr sheath and four balloons with an outer lumen of 4 mm serially arranged at the distal catheter end. The shaft itself contains three lumens: two smaller ones for the coolant in- and outlets and one large central 6-Fr lumen for the delivery of a dedicated catheter for the MT procedure vessel such as a microcatheter for transport of a stent retriever, or a distal access catheter for direct clot aspiration (ADAPT), or a coaxial system for stent retriever plus distal aspiration MT. The balloons are in fluid dynamical connection with both in- and outlet lumens, with coolant flowing to the catheter distal tip and then backward through

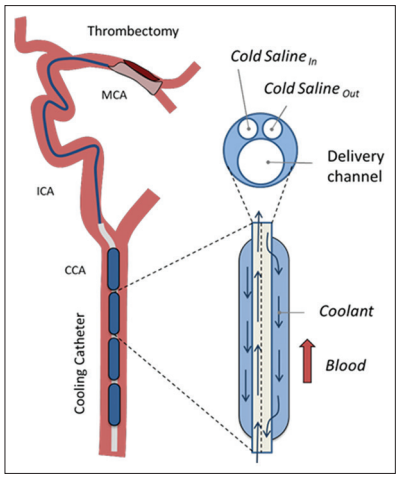

Figure 1: Schematic depiction of the cooling catheter construction and flow direction of coolant within the balloons. Heat exchange between bold and coolant occurs in counterflow, with coolant flowing within a catheter inlet lumen to the distal tip and then back within the outlet lumen

the balloons serially, providing a counter-flow heat exchange with the bypassing bloodstream inside the carotid artery.

The application of the intracarotid cooling catheter in the frame of a neurovascular MT procedure for vessel recanalization is described in Figure 2. Furthermore, an extracorporeal cooling unit is needed for heat exchange with the coolant. In the experiments described below, the unit consists of a roller pump for providing coolant flow and a compressor chiller, which extracts heat from the coolant on a conductive way, without fluid contact. The coolant is transported to and removed from the catheter by means of a tubing set connected to two ports at the proximal catheter end.

The catheter system aims at performing blood cooling in three phases of the procedure:

1. Prereperfusion cooling: The cooling catheter is placed within the carotid artery. Thereby the cooling catheter replaces a standard long sheath used for MT access to the intracranial circulation, no additional step in the procedure is performed. As soon as the catheter is placed, coolant flow is activated by means of an external roller pump combined with a chiller, and heat exchange with blood flowing within the carotid artery begins. Since the vessel distal to the occlusion cannot be perfused, cold blood reaches the hypoperfused penumbral brain tissue through collateral arteries such as the leptomeningeal anastomoses from the anterior to the middle cerebral artery (MCA) in case of a proximal MCA occlusion. During this stage of the procedure, catheters and devices for the recanalization of the MT procedure are advanced distally through the delivery lumen targeting the occluding clot. Thus,

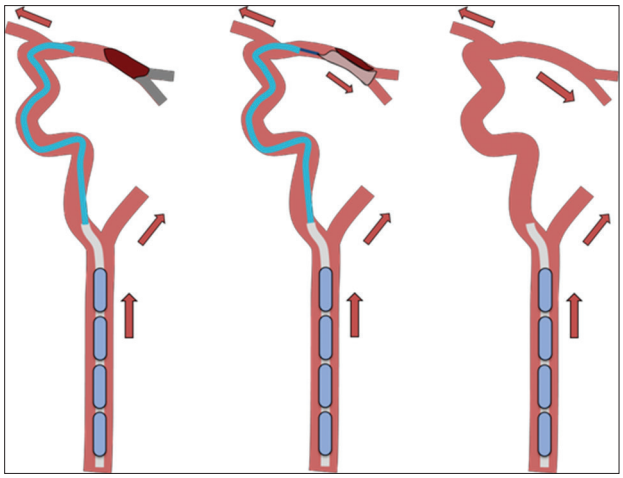

Figure 2: Schematic depiction of combined mechanical recanalization of media cerebral artery and intracarotid cooling for intra- and postischemic local brain hypothermia. Cooling of blood flowing into the brain occurs in three different phases: During endovascular procedure and before final vessel recanalization through collateral vessels arising from the external and internal circulation (left); during mechanical thrombectomy through the recanalized media cerebral artery and collaterals (middle); after removal of thrombectomy catheters through the recanalized media cerebral artery and collaterals (right)

neuroprotection may be already provided during the start of the procedure before vessel recanalization, potentially providing a very early neuroprotection and thus extending the therapeutic time window for MT, particularly if access to the clot is prolonged by difficult vascular anatomical conditions or by thrombus adhesion to the vessel wall.

2. Intra-reperfusion cooling: Directly after recanalization by means of MT or aspiration, the cold blood flows enter the recanalized vessel and downstream into the ischemic core tissue, providing a "cold reperfusion." This phase continues while the clot is pressed at the vessel wall and engaged by a stent-like device, during following distal angiography and during additional, potentially needed recanalization procedures (in case of ailed recanalization of distal embolism).
3. Postreperfusion cooling: The cooling catheter can potentially be kept inside the carotid artery after successful MT procedure for a certain amount of time continuing cooling of the blood that supplies the reperfused brain territory for prolonged early neuroprotection.

The depicted therapeutic concept potentially allows for a SBH without detrimental effect on the MT procedure of vessel recanalization, which should not be delayed or compromised as a Class Ia indicated therapy in case of a LVO stroke. Since the central delivery lumen should be dimensioned large enough for the delivery of recanalization catheter systems, smaller lumens for coolant flow need to be integrated into the limited remaining place within the catheter shaft, representing a trade-off between miniaturization and performance. For this reason, we performed extensive preclinical empirical as well as numerical evaluations to answer the following questions:

1. Which cooling performance can be provided by the catheter, assuming the size of the central lumen to be compatible to thrombectomy catheters and thus implementable into the standard procedure for vessel recanalization?
2. Which brain temperature results from the blood temperature reduction within the carotid artery? Is a mild hypothermia within the penumbra at the time point of recanalization and thus a "cold reperfusion" achievable?

Results of Preclinical Studies

Mathematical, numerical, and *in vitro* modeling: heat exchange with blood

The heat exchange between the coolant within the balloons and the surrounding blood occurs by conduction across the wall of the balloon, since in the closed-loop circuit, no transfer of coolant into the blood is provided. Furthermore, heat conduction and convection processes take place in both coolant and blood. The temperature gradient between coolant and blood is the force promoting the heat exchange. Coolant warms up by flowing within the balloons, with a stronger rewarming effect at lower flow rates, while blood cools down. While blood cooling is pursued, coolant temperature increase reduces the temperature gradient between blood and coolant and thus the acting force for heat exchange. For this reason, with the objective of a high heat exchange performance, a high coolant flow rate with consideration of the lumen size should be aimed. In the theoretical and experimental studies, both coolant channels have a diameter of around 1 mm each, which is compatible with the catheter outer dimension (~3.3 mm diameter, corresponding to an 8-Fr sheath) and size of central lumen compatible with 6-Fr catheters for mechanical aspiration. According to pressure drop in the channels, a flow rate of 100 ml/min is feasible with the use of high-performance roller pump systems.

Mathematical models showed that while the balloon wall thickness plays a minor role, contributing to around 5% to 10% of heat exchange resistance, depending on balloon configuration.[6] In contrast, flow-dependent convective processes strongly influence the heat exchange processes. Numerical simulation, as well as *in vitro* test in a mock loop of intracarotid circulation with a blood substitute with different catheter designs, revealed a higher heat exchange for a higher number of shorter balloons, while keeping the exchange surface constant, which is attributable to boundary layer disruption and thus increase of convection.[5]

The increase of balloon diameter led to an improvement of heat exchange surface and at the same time influences convective exchange processes at both coolant and blood side.[6] Since the nonocclusive nature within the carotid artery is a main requisite, diameter was chosen in a size of around 4 mm, which causes a minor flow resistance according to fluid dynamical calculations.

In vitro, catheter prototypes manufactured four serially arranged balloons with a diameter of 4 mm resulting in a temperature drop of almost 2.2°C at a blood substitute flow rate of 250 ml/min. For the reason depicted above, temperature reduction is less pronounced for higher blood substitute flow rates (1.6°C at a flow of 400 ml/min). Translated into the clinical scenario of large artery occlusion stroke, where carotid perfusion rate may be influenced by a downstream vessel occlusion, this represents an important variable affecting the velocity of temperature drop in the target brain regions.

In vivo Testing

Theoretical and *in vitro* results presented above the focus of blood cooling but do not consider resulting temperature reduction in brain resulting. In a first *in vivo* study, cooling catheters were navigated into the carotid arteries of nine sheep and balloons flushed with cold saline as a coolant for 3 h, while brain temperature was measured by intraparenchymal probes.[7] Tests showed a significantly stronger reduction of brain temperature in the ipsilateral hemisphere compared to the contralateral hemisphere and to systemic temperature. Within a time of nearly 30 min, an ipsilateral temperature drop of 2°C, compared to around 1°C in the contralateral side, was measured. After the first 15 min, where brain temperature dropped steeper compared to systemic temperature, brain and systemic temperatures continued to equally decrease maintaining a gradient of around 1.1°C over 4 h of intracarotid blood cooling.

Since this study does not consider the perfusion impairment during ischemic stroke, a second study was performed for comparison of temperature curves as well as safety issues in ten normothermic and ten hypothermic sheep using an ischemic stroke model with temporary MCA occlusion. The cooling catheter was optimized to allow the delivery of a 6-Fr distal aspiration catheter within the central lumen. Results, which are still not published, indicate a considerable increase of the cooling performance achieved by means of design optimization of the coolant lumens.

Numerical Perfusion Model

Although the sheep animal model is useful for *in vivo* investigation of the endovascular catheter system in a biological environment, it has crucial limitations due to anatomical differences in blood supply between ovine (rete mirabile) and human brain (carotid siphon). A numerical model was developed to predict the temperature reduction in the human brain during blood cooling with consideration of human anatomy as well as different perfusion states within the penumbra during cerebral ischemia. Time to reach a temperature drop of 2°C was in 8.3 min in case of a physiological perfusion rate of 50 $\frac{ml}{100g \cdot min}$ but increased to 26.2 min for a reduced perfusion of 10. $\frac{ml}{100g \cdot min}$ Moreover, in the case of a vessel recanalization after 10 min, leading to a sudden increase of perfusion rate from 10 to 50 $\frac{ml}{100g \cdot min}$, 2°C was reached after 14.5 min. In the numerical modeling, results of *in vitro* tests (2.2°C blood cooling at 250 ml/min blood flow within the carotid) were implemented in the calculation (semi-empirical approach).

Discussion

While blood cooling within the carotid artery seems to be a meaningful and promising approach to achieve a fast SBH, several other endovascular approaches are possible and were investigated in preclinical and clinical studies.

Cold saline infusion

Among all techniques, intracarotid infusion of cold saline has been suggested as a practicable and effective cooling method and was investigated in animal experiments as well as in human studies with AIS patients. In the studies using rat models summarized in Table 1, local hypothermia produced by cold saline infusion correlated with a reduction of the infarct size, whereas the effect was stronger if the start of cooling was previous to induction of ischemia or to vessel recanalization. Moreover, in the case of pre- or intra-ischemic cooling, a limited duration of hypothermia of <1 h demonstrated a neuroprotective effect.

Clinical application of cold saline infusion in AIS patients was also promising, as it demonstrated safety when cold saline was administered after MT by means of the 2.4-F microcatheter used for the delivery of the thrombectomy system.[8] A recent nonrandomized cohort study with 113 AIS patients with LVO used the same microcatheter-based protocol: 50 ml of 4°C cold 0.9% saline infused into the ischemic territory at 10 ml/min before recanalization plus further reinfusion of cold saline into the ischemic brain directly after MT at a rate of 30 ml/min for 10 min. This study reported a promising small but significant reduction of infarct volumes with trend toward increased

Table 1: Investigation of selective brain hypothermia in small animal models: Summary of methods and results

Quelle	Model	Experimental groups	Control groups	Temperatures (brain)	Outcome
Wang, *et al*. Comparison of neuroprotective effects in ischemic rats with different hypothermia procedures. Neurol Res 2010,32:378-83	Sprague-Dawley rats (64x) 3-h MCA occlusion using intraluminal filament (verification through neurological deficits) T-measurement: Intracortical thermistor probes, rectum (1) 48 h histological examination of infarct volume 2) Motor behavior at 14 and 28 days	(1) Infusion cold saline (20°C) after 3 h Ischemia before onset of reperfusion	(2) External systemic cooling before onset of reperfusion (reperfusion delayed by 30 min until target temperature was achieved) (3) External head cooling before onset of reperfusion (reperfusion delayed by 15 min? Until target temperature was achieved) (4) Normothermic	(1) 33.5°C at reperfusion, ~34°C for 20 min, back to 37°C within 60 min (2) Similar to (1), but with systemic effect (3) <33°C for 5 min, then back to baseline	Infarct volumes (1) Cold saline: 10% (2) External systemic: 30% (3) External head: 37% (4) Normothermic: 55% Similar trend in neurological scores: Significant improvement in (1), then (2), and (3)
Ding, *et al*. Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rat with Transient meddle cerebral artery occlusion. Neurosurgery 2004,54:956-65	Sprague-Dawley rats 3-h MCA occlusion using intraluminal filament (verification through neurological deficits) T-measurement: Intracortical thermistor probes, rectum 1) 48 h histological examination of infarct volume (1, 2, 3, and 4) 2) Motor behavior at 14 and 28 days (1, 4, and 5)	(1) 10 min infusion of 6 ml cold saline (20°C) before onset of reperfusion	(2) Cold saline through femoral artery (3) Local saline infusion at 37°C (4) Stroke without infusion (5) Normal control animals	(1) 33.4°C at reperfusion, ~34°C for 20 min, back to 37°C in 60 min (2) 35.3°C at reperfusion, back to 37°C in 10 min Rectal: Same effect in (1) and (2), ~36.5°C at reperfusion and back to baseline in 20 min	(1) 3.8% infarct volume in local cooling (2) 43,4% in systemic cooling and (3-4) ~54% in normothermia Neurological score in (1) compared to control (5) and significantly improved compared to (4)
Maier, *et al*. Delayed induction and long-term effects of mild hypothermia in a focal model of transient cerebral ischemia: Neurological outcome and infarct size. J Neurosurg 2001;94:90-6	Sprague-Dawley rats 2-h surgical ligation of CCA, ECA, and pterygopalatine artery, stroke production with multifilament suture 18-23 mm from bifurcation Spraying alcohol and fan, 2 h hypothermia at 33°C Rectal temperature measurement, no intracranial temperature measurement: Tbrain=Trectal+0.2°C-0.7°C (assumption) 3 days survival, behavioral (24 h and 72 h), and histological (72 h) analysis	(1) Hypothermia 33°C at stroke onset (*n*=11) (2) Hypothermia 33°C 90 min after stroke onset (*n*=10) (3) Hypothermia 33°C 120 min after stroke inset (*n*=10) (4) Hypothermia 33°C 180 min after stroke onset (*n*=5)	(5) Normothermia (*n*=23)	33°C rectal	Significant neurological improvement in (1), (2), (3) versus (5) No improvement in postischemic hypothermia (4) Large infarct reduction (~60%) in (1) and (2) (similar reduction) in cortex, hemisphere, and striatum and in (3) but only in cortex No significant effect for (4) (only a trend)
Kurasako *et al*. Transient cooling during early reperfusion. J Cereb Blood Flow Metab 27:1919-30	Spontaneously hypertensive rat Ischemia: MCA snared with a 80-µm hook, CCA fitted for 1.5 h (the model aims at low or no collateralization) Three probes in MCA territory, one probe contralateral, epidural, rectal thermistor 2-h hypothermia 5 min before recirculation, rectal to 32°C with wet ice pack, pool of saline overlying the exposed MCA artery cooled at 28°C, 30°C, and 32°C Survival 24 or 72 h	(1) Saline drip 28°C (2) Saline drip 30°C (3) Saline drip 32°C	(4) Normothermic	Measured at three intracortical sites, between 28°C and 32°C	No significant improvement of infarct lesion in (3) at both 24 h and 72 h Significant infarct reduction at 72 h in (1) and nonsignificant reduction in (2) Same trend (but not significant) for (1) and (2) at 24 h

MCA: Middle cerebral artery, CCA: Common carotid artery, ECA: External carotid artery, Quelle = Literature (or source)

functional independence warranting the initiation of a larger RCT trial. However, there are some issues and challenges with this approach. First, coolant flow rate and total coolant amount injected have to be accurately defined in a trade-off between performance (high flow rate reduces the coolant rewarming within the aorta and increases the mixing temperature of blood and coolant at the catheter outlet) and safety issues as hypervolemia and hematocrit reduction. Furthermore, cold infusion through the microcatheter before MT may delay the time-dependent strong effect of vessel recanalization. In this regard, a recently presented novel 7.8-F insulated catheter (Khione, FocalCool, Mullica Hill, New Jersey, USA) that can be inserted into the carotid artery to transport a microcatheter for cold saline infusion appears very appealing. Compared to standard catheters not designed for tissue cooling, this system can provide 2–3 times greater cooling performance at clinically relevant infusion rates (10–40 ml/min) owing to its approximately 10°C colder delivery temperatures.[4] Thus, the induction of SBH may be faster and requires less fluid to reach target temperature, thereby limiting the risks of hemodilution. In a recently published proof-of-concept study, this catheter system was tested in a canine model of transient MCA occlusion exhibiting excellent tissue cooling rates in the ipsilateral hemisphere (2.2°C/min) with a short duration of infusion (5 min before recanalization plus 20 min postrecanalization) and dramatic reduction of infarct volumes and minimal systemic impact (Caroff *et al*. JNIS 2019). Further preclinical and clinical research in SBH should be focused on the effect of timing and injected coolant volume on the cardiovascular system and on brain infarct progression. If high flow rates and volumes prove to be safe, lower temperature and longer duration of hypothermia could be achieved and coolant infusion would have a high potential as a relatively simple method to provide SBH in the setting of MT therapy in LVO stroke patients.

Extracorporeal cooling

In the method suggested by Mattingly *et al*., a coaxial catheter system (TwinFlow; Thermopeutix) is used to drain blood from the aorta and feed it back to selectively perfuse the common carotid artery with cooled blood. Inlet and outlet openings at the catheter tip are separated by an occluding balloon to avoid a short closed-loop effect and to separate the carotid from warm systemic circulation. A heat exchanger for blood cooling is integrated into the extracorporeal circuit, as well a blood pump promoting the blood within the two-lumen system. Based on components for assisted extracorporeal circulation, this extracorporeal system presents a much higher heat exchange, thus allowing for higher blood temperature reductions than any implantable heat exchange system. A temperature of <30°C, corresponding to severe brain hypothermia, was achieved within 30 min with a significant reduction of infarct volumes in a swine MCA occlusion model.[9]

Despite this excellent performance, crucial limitations are expected in the frame of a AIS treatment, since extracorporeal circuits require larger catheter dimensions (outer diameter, 14 F) and additional time for the set-up[10] (cit, letter to the editor). Moreover, they demand high heparin doses which can be deleterious in case of postreperfusion hemorrhage. Moreover, carotid occlusion and active blood pumping elude the mechanisms of flow regulation, potentially leading to high pressures in hypo- and normoperfused areas of the brain. Last, for blood circulation, two large catheter lumens are required to reduce the shear stress and thus to avoid hemolysis. For this reason, an extra lumen for MT access is not integrated within the catheter and cooling can be performed only after the removal of MT catheter system.

Intracarotid Closed-Loop Catheter

Differently than in direct coolant infusion, the intracarotid closed-loop catheter provides a blood temperature reduction by means of heat conduction across the balloon walls without any fluid mixing. Like in coolant infusion, a high coolant flow rate favors blood cooling. The reason is a rewarming effect of coolant within the balloons, which reduces temperature gradient between coolant and blood and is more pronounced at low flow rates. On the other side, differently than in coolant infusion, high coolant flow rates do not lead to hypervolemia and hematocrit decrease. The upper limit to coolant flow rate is represented by the lumen size, which is dependent from the outer dimension of the catheter and the size of the integrated lumen for thrombectomy. According to *in vitro* tests, a coolant flow of 100 ml/min allows for a blood temperature drop of around 2°C at a blood flow of 250 ml/min. Although this value is lower than in both alternative methods, cooling can be potentially kept for a longer time. A further consideration has to be made with regard to the effect of cooling catheter on the procedural aspects of MT. Although catheter dimensions provide a compatibility with distal aspiration catheters for neurovascular access and MT, the current design does not include an occlusion balloon for proximal flow arrest supporting clot retrieval. Since the cooling balloons with a diameter of 4 mm are not conceived to be occlusive, a potential extension of the catheter with an occlusive balloon would be needed to enhance future treatment options.

Final consideration

There are many factors which potentially influence the effects of SBH by means of intra-arterial cooling. First, the timing of the onset of cooling: if the MT procedure

takes a long time due to anatomical complexity in endovascular access or difficulty to retrieve the clot and recanalize the occluded vessel, an intra-ischemic cooling through collateral arteries feeding the penumbra could be a successful strategy to potentially enlarge the time window for recanalization. In other words, SBH would provide a "background" neuroprotection during time-critical recanalization procedures. In this case, direct cooling within the intracarotid artery should be preferred or at least combined to cold infusion distally to the thrombus, which would occur later during recanalization. Furthermore, velocity and duration of cooling are important factors, particularly in direct coolant injection. In rodent stroke models, a neuroprotective effect after 1 h of cooling was shown. At a volume rate of 33 ml/min, which was suggested by Choi *et al.*,[11] a coolant volume of 2 L would be applied in 1 h. Effect of hypervolemia, possible pressure increase, and reduced hematocrit in this time frame should be analyzed. One the other side, coolant infusion could potentially provide a potential benefit in terms of flushing inflammatory cells. Finally, in both approaches, design aspects such as a dedicated insulation of catheter systems to reduce heat transfer within the aorta (causing a rewarming of the coolant) may be crucial to provide a faster and higher temperature drop at smaller total infusion volumes.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Cattaneo was employed at Acandis, involved in the development of the catheter, and now is a consultant of Acandis.

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