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ABSTRACT

BACKGROUND AND PURPOSE: Therapeutic hypothermia represents a promising neuroprotective treatment in acute ischemic stroke. Selective cerebral hypothermia applied early, prior to and during endovascular mechanical recanalization therapy, may be beneficial in the critical phase of reperfusion. We aimed to assess the feasibility of a new intracarotid cooling catheter in an animal model.

MATERIALS AND METHODS: Nine adult sheep were included. Temperature probes were introduced into the frontal and temporal brain cortices bilaterally. The cooling catheter system was introduced into a common carotid artery. Selective blood cooling was applied for 180 minutes. Systemic and local brain temperatures were measured during cooling and rewarming. Common carotid artery diameters and flow were measured angiographically and by Doppler sonography.

RESULTS: The common carotid artery diameter was between 6.7 and 7.3 mm. Common carotid artery blood flow velocities increased moderately during cooling and after catheter removal. Maximum cerebral cooling in the ipsilateral temporal cortex was −4.7°C (95% CI, −5.1 to −4.0°C). Ipsilateral brain temperatures dropped significantly faster and became lower compared with the contralateral cortex with maximum temperature difference of −1.3°C (95% CI, −1.5 to −1.0°C; $P < .0001$) and compared with systemic temperature (−1.4°C; 95% CI, −1.7 to −1.0°C; $P < .0001$).

CONCLUSIONS: Sheep proved a feasible animal model for the intracarotid cooling catheter. Fast induction of selective mild hypothermia was achieved within the cooled cerebral hemisphere, with stable temperature gradients in the contralateral brain and systemic blood. Further studies are required to demonstrate any therapeutic benefit of selective cerebral cooling in a stroke model.

ABBREVIATIONS: BW = body weight; CCA = common carotid artery; ΔT = temperature drop; MT = mechanical thrombectomy; TH = therapeutic hypothermia

Therapeutic hypothermia (TH) is an established neuroprotective therapy in patients after cardiac arrest[1] and in neonates with severe asphyxia.[2] Recently, the feasibility and safety of TH in patients with acute ischemic stroke was proved in controlled studies,[3-6] and 2 multicenter, randomized clinical trials (EuroHYP-1 and ICTuS 2/3)[7,8] are currently underway to study its efficacy.

Patients with stroke with large-artery occlusions benefit from endovascular recanalization by mechanical thrombectomy (MT).[9-13] However, reperfusion of ischemic brain tissue may induce additional damage and hemorrhagic transformation, potentially limiting the benefits of recanalization. Current systemic cooling approaches involve long induction times, so the time window for TH during the critical reperfusion phase may still be missed for many patients.[14]

Recently, we have developed an intracarotid cooling catheter system for combined MT and selective TH treatment.[15] It simultaneously serves as an access for the intracranial MT procedure and enables early cooling of the ischemic penumbra via collaterals before recanalization, to then provide a "cold reperfusion" of the ischemic core during and after MT treatment. The latter is expected to be a critical determinant of clinical outcome.[7] Moreover, selective cooling may reduce systemic adverse events from TH.

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In this study, we aimed to assess the feasibility of the new cooling catheter in a large animal model with continuous monitoring of systemic and local cortical brain temperatures.

MATERIALS AND METHODS

Balloon Cooling Catheter System

The in vitro development and optimization of the intracarotid balloon cooling catheter system (Acandis, Pforzheim, Germany) was previously described.[15] In this study, the device and its functional properties were extensively outlined, including photographic and schematic images of the balloon cooling system. It consists of 4 serially arranged balloons at the catheter tip (diameter, 4 mm; length, 20 mm each) perfused with coolant (0.9% sodium chloride) that connect to a closed-loop inner-catheter cooling circuit without direct blood contact. The latter is kept constant at ~6°C provided by an external thermostat and circulated by a roller pump. A third lumen (diameter, 1 mm) allows passage of a 2.5F microcatheter and thus distal access for MT.

Animal Studies

Animal experiments with 9 sheep were approved by the local ethics committee (Freiburg, Germany) and performed in accordance with the German animal protection law and the animal care guidelines of the European Community (2010/63/EU).

Under general anesthesia (see protocol below), temperature probes (MP00991; Dräger Medical, Lübeck, Germany) were introduced into the frontal and temporal brain cortices bilaterally by neurosurgical burr-hole craniotomies. Via transfemoral arterial access, the cooling catheter system was introduced through an 8F 90-cm sheath (Flexor Shuttle Guiding Sheath; Cook, Bloomington, Indiana) into the common carotid artery (CCA) under systemic heparinization (70 IU/kg body weight [BW]) and fluoroscopic guidance. Selective intracarotid blood cooling was applied by coolant circulation and maintained for 60 minutes in the first sheep and 180 minutes in the remaining 8 sheep. Cortical brain, nasal, and systemic (inferior vena cava) temperatures were measured at 10-second intervals during cooling and 30 minutes after catheter removal. CCA diameters were measured by Doppler sonography and DSA before catheter insertion. During cooling and after catheter removal, the patency and flow of the CCA and side branches were assessed on DSA at 30-minute intervals. Blood temperature distal (1, 5, and 10 cm) to the cooling catheter was measured by using a self-made microprobe at 30-minute intervals. Mean blood-flow velocities were measured in mid-CCA on Doppler sonography before cooling catheter insertion, during cooling, and after cooling catheter removal. Positioning of brain temperature probes was analyzed on postprocedural CT.

Protocol of Animal Anesthesia

Adult sheep (80.2 ± 7.4 kg BW) were premedicated with intramuscular midazolam (0.5 mg/kg BW) and ketamine hydrochloride (20 mg/kg BW) and anesthetized intravenously with propofol (2–4 mg/kg BW). Following endotracheal intubation, 12–15 breaths/min were provided by a volume-controlled ventilator at a 10–15 mL/kg BW tidal volume, 5-mbar positive end-expiratory pressure, with setting adjustments to normalize oxygen and carbon dioxide tension and pH values. Anesthesia was maintained intravenously with propofol (15–18 mg/kg BW/h) and fentanyl (2–3 μg/kg BW/h). Fluid requirements were substituted with Ringer solution (10 mg/kg BW/h). Electrocardiogram, blood pressure, and oxygen saturation were monitored continuously. At the end of the experiment, sheep were sacrificed in deep anesthesia with an intravenous dose of potassium chloride.

Statistical Analysis

Statistical analyses were performed by using SAS 9.2 (SAS Institute, Cary, North Carolina) for data from 8 sheep with a 3-hour cooling phase. For each animal and temperature probe, temperature drops (ΔT = recorded temperature − baseline temperature) were calculated. Baseline temperatures were defined as time-averaged temperatures over 20 minutes before initiation of cooling. Temperature drops were averaged over the cooling phase and were compared within a linear regression model, accounting for repeated measurements by using the generalized estimating equation method for parameter estimation, with an exchangeable working correlation. The standard generalized estimating equation methodology provides robust standard error estimates that are reported here. We compared the cooled hemisphere versus the noncooled hemisphere (averaged frontal and temporal measurements), the cooled hemisphere versus the inferior vena cava, and the cooled hemisphere versus the nasal temperature. Mean temperature gradients (95% CI) were calculated between the cooled hemisphere and the noncooled hemisphere and systemic references during cooling and after 30 minutes of rewarming. Times needed to reach temperature drops of −1°C and −2°C were compared between measurement sites by using the Student *t* test.

RESULTS

The mean CCA diameters were 7.3 ± 1.0 mm proximally and 6.7 ± 1.0 mm distally on DSA and 6.3 ± 0.6 mm in the midsegment on sonography. Mean CCA blood flow velocity was 36.9 ± 8.2 cm/s, 51.9 ± 18.7 cm/s, and 55.8 ± 13.7 cm/s before cooling catheter insertion, after the start of cooling, and after balloon catheter removal, respectively. Mean baseline temperatures varied between 37.0°C ± 1.4°C and 37.2°C ± 1.7°C (3/9 sheep were shorn). During selective cooling, temperatures decreased significantly more in the cooled brain hemisphere versus the noncooled brain hemisphere ($P < .0001$) and versus central venous temperature ($P < .0001$) (Fig 1). The mean maximum ΔT was higher in the temporal cortex with −4.5°C (95% CI, −5.1 to −4.0°C) than in the frontal cortex with −4.2°C (95% CI, −4.7 to −3.7°C). The mean maximum systemic venous and nasal ΔTs were −3.5°C (95% CI, −3.9 to −3.2°C) and −4.0°C (95% CI, −4.7 to −3.4°C), respectively.

The mean maximum temperature gradient among the cooled-versus-noncooled hemisphere, systemic inferior vena cava, and nasal temperatures was −1.28°C (95% CI, −1.54 to −1.02°C), −1.37°C (95% CI, −1.71 to −1.04°C), and −0.79°C (95% CI, −1.08 to −0.49°C), respectively. After initiation of selective cooling, these temperature gradients increased rapidly to then remain relatively constant during the remaining cooling period (Fig 2). Immediately after cooling catheter system removal, the mean interhemispheric and hemispheric-systemic temperature gradients started to equalize with −0.15°C (95% CI, −0.40 to 0.09°C) and

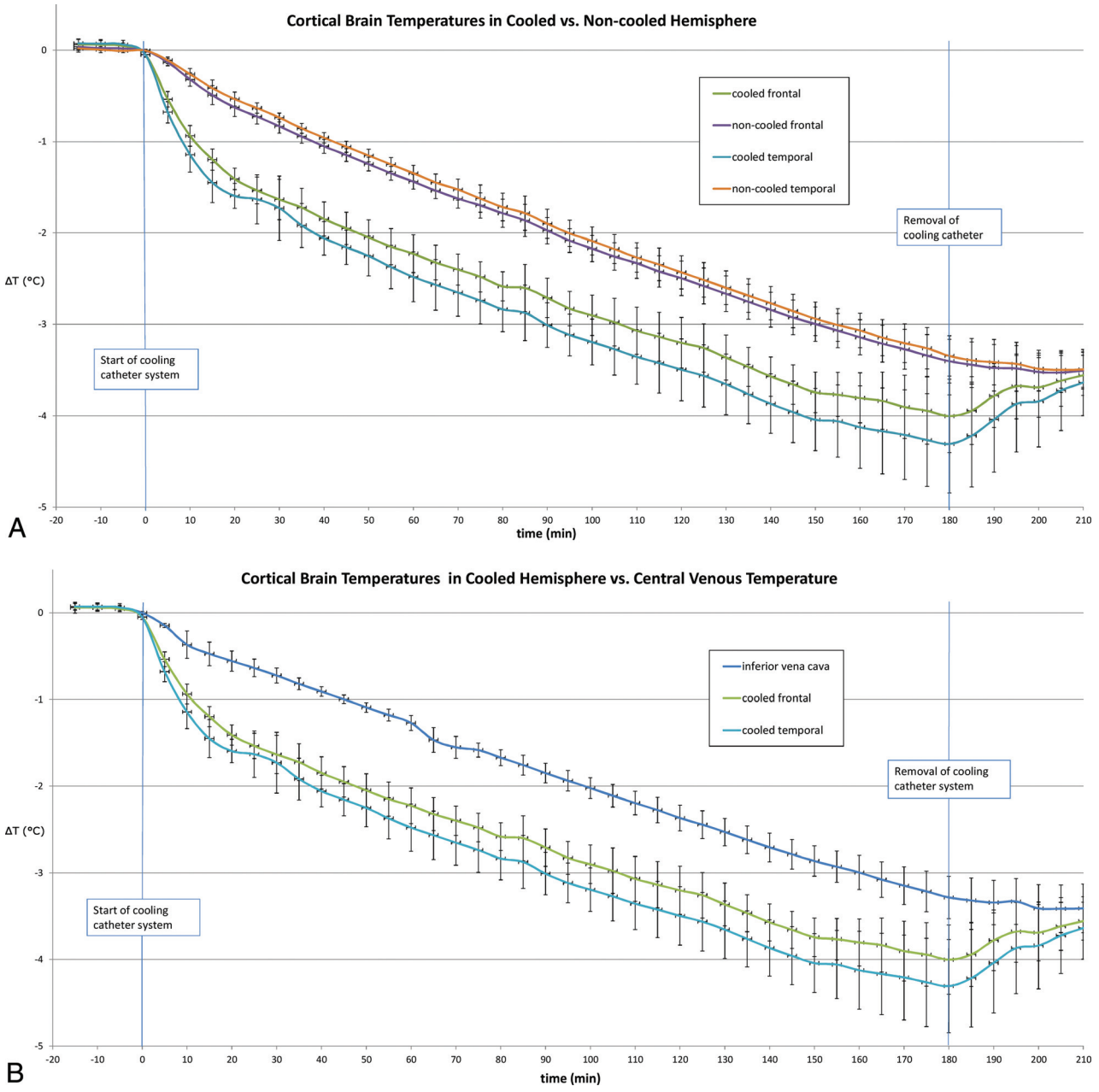

FIG 1. Temperature recordings from 9 sheep (mean ΔT and 95% CI, plotted at 5-minute intervals) that were measured during (0–180 minutes) and after (180–210 minutes) selective intracarotid blood cooling in the frontal and temporal cortical probes of the cooled-versus-noncooled hemisphere (*A*) and cooled-versus–central venous temperature (*B*), respectively.

−0.21°C (95% CI, −0.46 to 0.05°C), respectively, measured after 30 minutes of rewarming, while the systemic temperatures remained below −3°C to baseline temperature.

The velocity of cooling was initially the highest (pronounced in the temporal cortex) and then remained relatively constant during the cooling phase (Table). The times to reach −1°C and −2°C were significantly shorter in the cooled hemisphere compared with both the noncooled hemisphere ($P < .0001$) and the systemic venous temperature ($P < .0001$) and were marginally shorter compared with the nasal temperature ($P = .48$ and $P = .03$, respectively). Blood temperature at a 10-cm distance to the cooling catheter tip closely matched the cooled brain temperature during the later steady-state cooling phase (after ≈60 minutes, Fig 3).

On DSA, no evidence of CCA flow stagnation/occlusion or thromboembolic side branch occlusion was present. In 1 case, a superficial temporal branch occlusion related to the temporal craniotomy procedure was evident. In another case, the tip of the cooling catheter was accidentally engaged into a small muscular side branch of the CCA, resulting in branch occlusion after catheter withdrawal and major CCA vasospasm, whereas the latter resolved completely during further controls. In 6/9 sheep (66.7%), mild luminal changes compatible with vasospasm related to cooling catheter balloons (5/9) or tip (1/9) were found. Technical problems were the following: 1 temperature probe recording failure and, in 2 cases, short episodic rewarming (≈10 minutes) due to a torqued cooling catheter connection and shivering from shallow sedation.

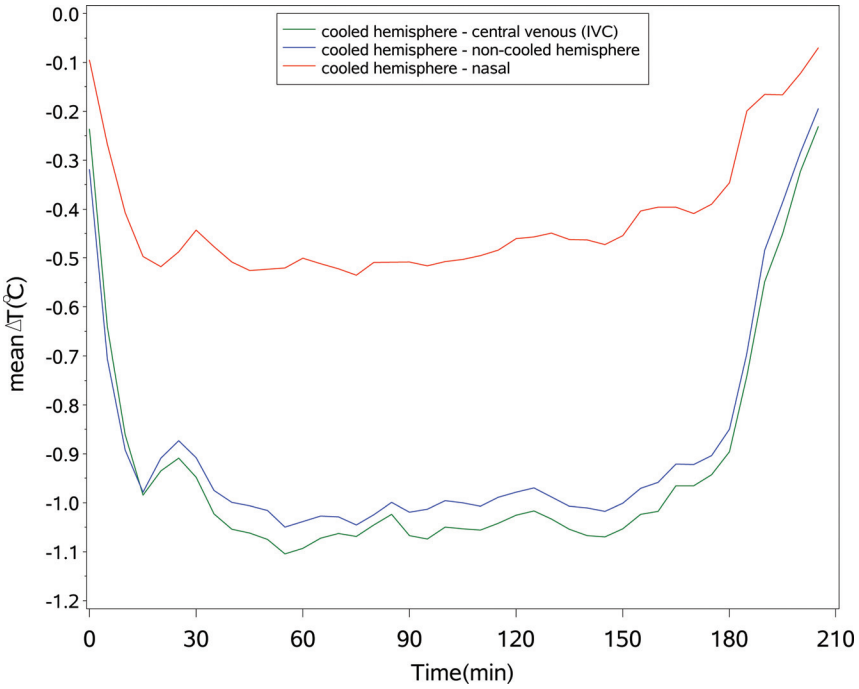

FIG 2. Mean temperature gradients (averaged over 8 sheep) among the cooled hemisphere and the central venous temperature, noncooled hemisphere, and nasal temperature, respectively, during 180 minutes of cooling and 30 minutes of rewarming (time-averaged at 5-minute intervals).

Velocity of selective brain cooling

	Cooled Temporal Cortex (median time) (range) (min)	Cooled Frontal Cortex (median time) (range) (min)
−1°C	8.5 (3.8–12.5)	11.5 (7.5–14.0)
−2°C	29.4 (11.7–70.3)	40.7 (27.0–70.0)
−3°C	85.7 (59.8–137.6)	100.5 (84.3–140.3)
−4°C	142.1 (109.3–180.0)[a]	158.3 (148.8–180.0)[a]

[a] −4°C was not reached in 2/8 sheep in both temporal and frontal cortices.

CT analysis of brain temperature probes showed optimal positioning of probes in 22/27 (81.5%); 2/27 (7.4%) were close to the craniotomy site; and 3/27 (11.1%) were close to midline. None were dislocated extracranially or crossed the midline.

DISCUSSION

In this in vivo study, we demonstrated the feasibility of selective cerebral hypothermia by using a newly developed intracarotid blood-cooling catheter system. The sheep is a suitable large-animal model with CCA diameters comparable with those of humans. The selective brain hemispheric temperature drop was induced significantly faster compared with the noncooled hemisphere and systemic temperature. The target temperature of 35° for mild TH (assuming a baseline temperature of 37°C) was achieved within a practical timeframe of 30–40 minutes for an MT procedure. Thus, these results may support the use of this catheter system in combination with MT for large-vessel occlusions to achieve an enhanced neuroprotective effect during the reperfusion phase ("cold reperfusion"). The latter concept remains to be proved in humans; however, various preclinical animal studies have indicated an increased benefit of TH when initiated early during the intra-ischemic period compared with delayed induction in the postischemic period.[16-19] In particular, selective intracarotid cooling applied in the reperfusion phase has achieved a faster and deeper intracortical temperature reduction and an enhanced neuroprotective effect in a rat model compared with systemic blood cooling.[14,20]

Mack et al[21] used a similar closed-loop cooling catheter system (without a central "working" lumen) for systemic venous hypothermia (target temperature of 32°C, maintained for 6 hours) in a primate surgical large-artery occlusion and reperfusion stroke model. In their study, cooling was initiated 2 hours after reperfusion (3 hours after the start of ischemia) without any demonstrated neurologic benefit. These negative clinical results may also support the hypothesis that selective early TH with the concept of "cold reperfusion" may be more beneficial in patients with acute stroke.

Besides selectivity, systemic cooling due to cold venous return also had an additive effect on the brain temperature drop, decreasing the catheter blood inlet temperature in our series. The lower cooling effect in the frontal-versus-temporal brain cortex can be attributed to blood mixing via the anterior communicating artery. The nasal temperature may only act as an imperfect surrogate of cooled brain temperature because it was measured in between the cortical brain temperatures of the cooled hemisphere and the systemic temperature, likely due to a mixture of cooled and noncooled blood supply via the ipsilateral and contralateral external carotid arteries.

Previous numeric modeling of selective brain cooling demonstrated the superiority of carotid artery blood cooling over external head-cooling devices.[22,23] Likewise, intracarotid cold saline infusion has been proposed for selective brain hypothermia by mathematic models,[24,25] and its effect was investigated on the jugular venous blood temperature in 18 patients undergoing diagnostic cerebral angiography.[26] The measured temperature drop (~0.8°C after 10 minutes of 7°C cold saline infusion at 33 mL/min) probably underestimates the true brain temperature due to blood mixing within the jugular venous return. We consider this technique an interesting alternative method for selective brain hypothermia and suppose that increasing the inflow rate of the coolant would increase the cooling performance. However, cold saline infusion may cause hemodilution and hypervolemia. The mathematic models cited above showed a decrease of the local hematocrit from 42% to 30.6% and ~20% after 60 minutes and 3 hours of saline infusion with a flow rate of 30 mL/min, respectively. In a randomized study of Kim et al[27] in patients with out-of-hospital cardiac arrest, 2 L of intravenous coolant at 4°C was given before hospitalization as soon as possible after return of spontaneous circulation in the hypothermia group. This resulted in an 11% higher rate of pulmonary edema and lower oxygen saturation on emergency department arrival. Although patients

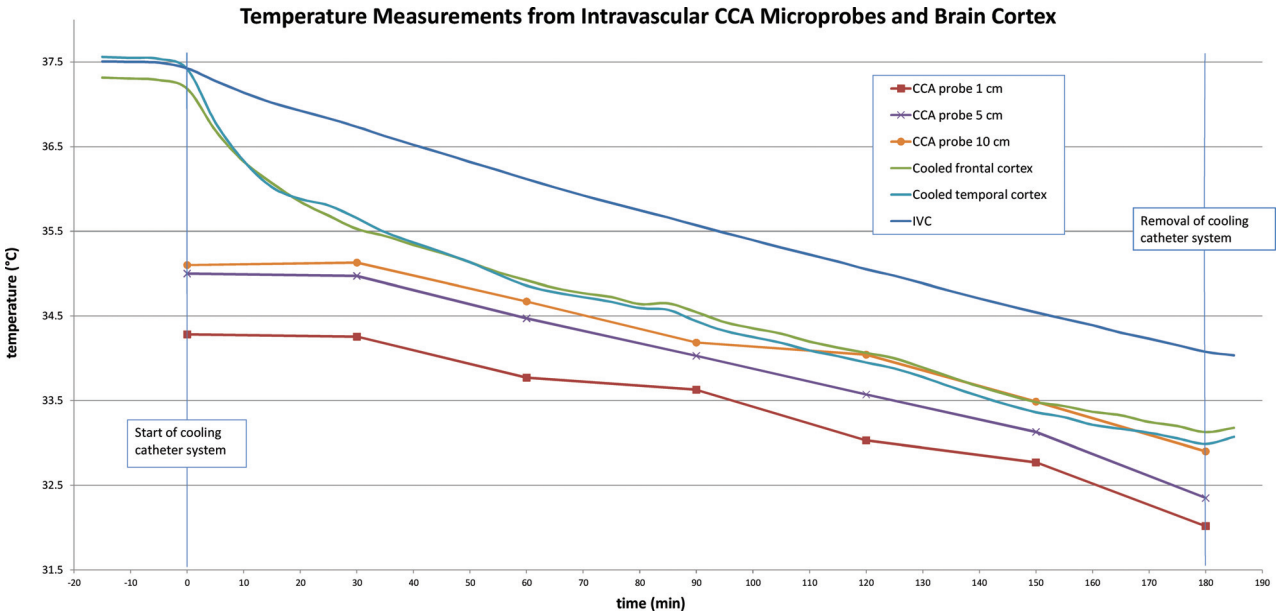

FIG 3. Microprobe temperature measurements performed at 30-minute intervals during the cooling phase at predefined distances to the cooling catheter tip (1, 5, and 10 cm) in comparison with continuously recorded ipsilateral brain cortex and central venous (IVC) temperatures.

with acute stroke may present with different clinical problems than those with cardiac arrest and the infusion rate may be kept lower, hemodilution and hypervolemia should be considered as possible relevant complications of cold saline infusions.

A recent study examined the induction of selective brain cooling (up to <30°C within 25 minutes) by means of a coaxial catheter system in a focal MCA branch occlusion stroke model in swine.[28] With this approach, the CCA was occluded by an inflated balloon catheter and isolated from the aorta. Intra-aortic blood was removed via the outer catheter, cooled, and pumped back into the CCA via the inner catheter lumen by an extracorporeal pump. Resultant infarct size (on MR imaging and histology) was significantly reduced in the hypothermia group. Schwartz et al[29] presented a different method of extracorporeal blood cooling in which the blood was withdrawn from the femoral artery and reperfused into the proximally occluded carotid artery. With this technique, selective brain hypothermia up to 25°C was induced with simultaneous maintenance of the systemic temperature at 36°C by warm water blankets and a substantial reduction of infarct size was demonstrated in a surgical ICA and anterior cerebral artery occlusion model with baboons.[30] We suppose that the large-bore catheters that were used in both approaches of endovascular intracarotid blood cooling[28,29] are needed for recirculation of the extracorporeally cooled blood and, therefore, are incompatible with simultaneous access to MT treatment. Thus, cooling may only be applied as a stand-alone treatment or delayed in the postreperfusion phase with these techniques. Hence, the latter represent major limitations in the context of MT treatment, which has become the standard of care for patients with acute large-artery occlusions. Moreover, the required high-dose heparinization during the 12-hour period of extracorporeal blood cooling and the artificial pump circulation through a proximally occluded CCA, potentially leading to detrimental cerebral hyperperfusion, may be further disadvantages of such approaches in the treatment of patients with acute stroke.

Our tested cooling catheter system may potentially overcome several limitations of other previously proposed approaches for selective TH: 1) closed-loop coolant circulation that avoids hemodilution and could allow longer cooling times compared with intracarotid cold saline infusion; 2) a central catheter lumen enabling access for MT of occluded intracranial arteries for patients with large cerebral artery occlusions, and 3) simultaneous "cold reperfusion" therapy without affecting cerebral perfusion pressures compared with extracorporeal blood cooling. The optimal target temperature of TH in acute ischemic stroke is still a matter of debate, whereas emphasis is put on the time window more than on the depth of cooling, with neuroprotection being proved at 35°C.[7] Otherwise, the variable flow conditions and collateral perfusion in patients with stroke with major artery occlusion and the different times to mechanical recanalization, which are very dependent on anatomy, will influence the temperature at and after reperfusion and cause a variability of the neuroprotective effect of the proposed method.

With regard to safety, no critical blood flow impairment or thromboembolic events were observed. The single dissection of a muscular side branch of the CCA was a procedural complication, which is rather unlikely to occur in the human CCA due to anatomic differences (no direct small CCA side branches).

We observed an increase of CCA blood flow velocities after insertion of the cooling catheter system, which was sustained (by approximately 50%) after removal of the catheter system. The former may be explained by a combination of blood flow obstruction due to the introduction of the catheter system itself and hypothermia, whereas, the latter is likely related directly to a vasodilation effect of the central arteries from hypothermia, which is in line with a study by Mahmood et al,[31] which showed an increase in MCA blood flow velocities in healthy volunteers after mild externally induced hypothermia (34.5°C). These findings are also supported by another experimental study demonstrating a cooling-induced reversible graded vasodilation of the rabbit ca-

rotid artery.[32] By contrast, studies of TH in patients with acute brain injury from hypoxia after cardiac arrest, severe MCA infarct, or severe traumatic brain injury or in patients with poor-grade subarachnoid hemorrhage and delayed cerebral ischemia mostly showed a reduction of cerebral blood flow.[33-37] However, under all latter pathologic conditions, a clear distinction between hypothermia-related and direct pathology-related effects on the CBF is impossible; this finding relativizes this discrepancy to our blood flow measurements in cooled but otherwise healthy animals.

A major limitation of our study was the testing of the cooling catheter system under physiologic blood flow conditions without ischemia from a cerebral large-artery occlusion. We have chosen such a nonischemic large-animal model to determine the in vivo feasibility and capacity for selective brain hypothermia of the developed cooling catheter system. For this application, the sheep model was found ideal because the catheter system may only be inserted into the carotid arteries of similar anatomic dimensions to a human CCA. Thereby, the risks and time of the surgical procedure were limited because the rete mirabile, which is the only access to the cerebral circulation in sheep, prevents the use of a clot for generating an MCA occlusion.[38,39] Moreover, the variability of collaterals may affect flow conditions under MCA occlusion among the animals, thus increasing the complexity of the model and complicating the interpretation of the temperature development under selective hypothermia. After successful demonstration of selective brain hypothermia, we will test the safety and efficacy of this technique for neuroprotection in a future surgical model of temporary MCA occlusion on sheep. Thus, our catheter-based, selective intracarotid cooling technique may also be compared with a control group undergoing systemic venous cooling.

CONCLUSIONS

Selective endovascular intracarotid blood cooling during 3 hours by using a new balloon cooling catheter system was able to achieve mild hypothermia (≈−4.5°C) in a sheep model with a faster and significantly deeper temperature drop in targeted brain hemisphere compared with contralateral brain and systemic temperatures. This selective intracarotid TH approach offers combined MT access in patients with acute stroke due to large-artery occlusion. Thus, it enables cooling of penumbral tissue as well as "cold reperfusion" during and after the MT procedure. As a next step, we will test the efficacy of selective TH in a modified sheep model of acute ischemic stroke due to middle cerebral artery occlusion.

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