SVN Stroke & Vascular Neurology

COmbination of Targeted temperature management and Thrombectomy after acute Ischemic Stroke (COTTIS): a pilot study

Jürgen Bardutzky ,[1] Rainer Kollmar,[2] Forat Al-Rawi,[1] Johann Lambeck ,[1] Mohammad Fazel,[3] Christian Taschner,[4] Wolf-Dirk Niesen[1]

To cite: Bardutzky J, Kollmar R, Al-Rawi F, *et al*. COmbination of Targeted temperature management and Thrombectomy after acute Ischemic Stroke (COTTIS): a pilot study. *Stroke & Vascular Neurology* 2023;**0**. doi:10.1136/svn-2023-002420

Received 27 February 2023
Accepted 5 August 2023

[1]Department of Neurology and Neurophysiology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[2]Neurology and Neurointensive Care, Darmstadt Hospital, Darmstadt, Germany
[3]BrainCool AB, Lund, Sweden
[4]Department of Neuroradiology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Correspondence to
Professor Jürgen Bardutzky; juergen.bardutzky@uniklinik-freiburg.de

ABSTRACT

Background To evaluate the feasibility and safety of a fast initiation of cooling to a target temperature of 35°C by means of transnasal cooling in patients with anterior circulation large vessel occlusion (LVO) undergoing endovascular thrombectomy (EVT).

Methods Patients with an LVO onset of <24 hour who had an indication for EVT were included in the study. Transnasal cooling (RhinoChill) was initiated immediately after the patient was intubated for EVT and continued until an oesophageal target temperature of 35°C was reached. Hypothermia was maintained with surface cooling for 6-hour postrecanalisation, followed by active rewarming (+0.2°C/hour). The primary outcome was defined as the time required to reach 35°C, while secondary outcomes comprised clinical, radiological and safety parameters.

Results Twenty-two patients (median age, 77 years) were included in the study (14 received additional thrombolysis, 4 additional stenting of the proximal internal carotid artery). The median time intervals were 309 min for last-seen-normal-to-groin, 58 min for door-to-cooling-initiation, 65 min for door-to-groin and 123 min for door-to-recanalisation. The target temperature of 35°C was reached within 30 min (range 13–78 min), corresponding to a cooling rate of 2.6 °C/hour. On recanalisation, 86% of the patients had a body temperature of ≤35°C. The median National Institutes of Health Stroke Scale at admission was 15 and improved to 2 by day 7, and 68% of patients had a good outcome (modified Rankin Scale 0–2) at 3 months. Postprocedure complications included asymptomatic bradycardia (32%), pneumonia (18%) and asymptomatic haemorrhagic transformation (18%).

Conclusion The combined application of hypothermia and thrombectomy was found to be feasible in sedated and ventilated patents. Adverse events were comparable to those previously described for EVT in the absence of hypothermia. The effect of this procedure will next be evaluated in the randomised COmbination of Targeted temperature management and Thrombectomy after acute Ischemic Stroke-2 trial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the success of endovascular treatment, more than half of the patients remain dependent. Fast initiation of hypothermia, which also covers the reperfusion phase, can help save penumbra tissue.

WHAT THIS STUDY ADDS

⇒ This novel cooling approach in thrombectomy patients was feasible and safe, and associated with very good functional outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The multicentre randomised-controlled COmbination of Targeted temperature management and Thrombectomy after acute Ischemic Stroke-2 trial (COTTIS-2) will evaluate the efficacy of this approach.

INTRODUCTION

Although endovascular treatment (EVT) is known to be beneficial in acute ischaemic stroke patients with large vessel occlusion (LVO) in the anterior circulation, more than half of these patients remain functionally dependent, despite the high reperfusion rates.[1 2] Indeed, infarct progression despite reperfusion is well documented in the literature[3] and is not unexpected given the progression in time. Furthermore, a substantial number of patients have been observed to develop reperfusion injury following successful recanalisation.[4]

Thus, new strategies such as hypothermia-induced neuroprotection need to be explored, not only to bridge the time to reperfusion but also to attenuate reperfusion injury. Therapeutic hypothermia has been demonstrated as a robust form of neuroprotection in animal ischaemic-reperfusion models.[5 6] Nonetheless, randomised trials in acute stroke patients have failed to demonstrate the efficacy of induced hypothermia compared with conventional treatment.[7]

The reasons for this treatment failure are diverse and include treatment delay, mainly due to elaborate and invasive cooling procedures; the infeasibility of inducing and maintaining hypothermia until the target

temperature is reached, mainly in awake patients and the lack of recanalisation in a large proportion of patients.[6–8]

By attaining high rates of recanalisation using EVT in sedated patients and applying improved methodology for the induction of hypothermia, the failure of hypothermia observed in previous acute stroke studies can potentially be overcome.[9]

Indeed, fever (>37.5°C) has been shown to have a negative influence on postprocedural infarct growth in acute ischaemic stroke patients undergoing EVT, despite successful reperfusion.[10 11] In addition, a higher body temperature during both the prerecanalisation and post-recanalisation phases were associated with poorer clinical outcomes in EVT patients.[12] In a recent observational study, the application of a short-duration, intra-arterial, selective-cooling infusion with 4°C saline for 5 min prior to EVT and 10 min after recanalisation was associated with a smaller infarct volume and a trend towards clinical benefit.[13]

In experimental and clinical efficacy studies with invasive brain temperature measurements, the transnasal cooling device RhinoChill resulted in a fast and uniform reduction of brain temperature in all parts of the anterior circulation.[14–16] The present study, therefore, aimed to investigate the feasibility and safety of a rapidly initiated cooling process to a target temperature of 35°C before recanalisation. This was achieved via transnasal cooling by RhinoChill, followed by surface cooling for 6 hour after recanalisation in intubated and sedated patients with LVO undergoing thrombectomy.

METHODS

Trial design

The present study is a prospective, single-arm, open-label clinical trial to assess the feasibility and safety of hypothermia induction by transnasal cooling before mechanical recanalisation immediately after EVT-dependent intubation, followed by surface cooling for 6 hours after recanalisation in patients with LVO.

The study was conducted at a single comprehensive stroke centre (CSC). Patients included were either admitted directly to the CSC or secondarily transferred from a primary stroke centre of the stroke network after diagnosis of LVO. The stroke network comprised 12 primary stroke centres and one CSC. Patients were enrolled from December 2021 until May 2022.

Written informed consent was obtained either from the patient or the patient's legal representative. If this was not possible, an independent physician who was not involved in the study gave informed consent in accordance with the patient's presumed wishes; subsequent written informed consent was obtained from the patient or the legal representative as soon as possible.

Patients

The inclusion and exclusion criteria are shown in box 1. In summary, acute stroke patients with moderate to severe ischaemic stroke (defined by a National Institutes of Health Stroke Scale (NIHSS) score of >5) caused by LVO, and who underwent thrombectomy within 24 hours of symptom onset according to the current European Stroke Organization guidelines[17] were enrolled in the study. Major exclusion criteria were severe coagulopathy, severe infection, brain trauma or neurovascular intervention <3 months prior to LVO.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- ⇒ Age >18 years.
- ⇒ Prestroke modified Rankin Scale score of 0–2.
- ⇒ Indication for endovascular treatment
  - ⇒ Acute ischaemic stroke with an NIHSS score >5.
  - ⇒ Intracranial occlusion of the M1 or M2 segment of the middle cerebral artery or internal carotid artery or tandem occlusion on CT/MR-angiography.
  - ⇒ Time window:
    - ⇒ Time from last known normal-to-groin-puncture <6 hours: native CT or MR-DWI with ASPECTS >5 (optional CT-perfusion or MR-perfusion).
    - ⇒ Time from last known normal-to-groin-puncture 6–24 hour or unknown time window: significant imaging mismatch according to the eligibility criteria of
    - ⇒ DEFUSE-3[35]: infarct core <70 mL (defined by CBF <30% or by MR-DWI), mismatch volume >15 mL (defined by the difference between Tmax >6 s volumes and infarct core), mismatch ratio >1.8.
    - ⇒ DAWN-trial[36]: infarct core defined by CBF <30% or by MR-DWI.
      - ⇒ ≥80 years and NIHSS >10: infarct core <21 mL.
      - ⇒ <80 years and NIHSS >10: infarct core <31 mL.
      - ⇒ <80 years and NIHSS >20: infarct core <51 mL.
- ⇒ With or without intravenous rtPA thrombolysis.
- ⇒ Written informed consent.*

Exclusion criteria

- ⇒ Known severe haemorrhagic diathesis (international normalised ratio >3.0, partial thromboplastin time >70 s, platelet count <50.000/µl).
- ⇒ Brain trauma or neurovascular surgery/intervention <3 months prior to LVO.
- ⇒ Severe infection.
- ⇒ Life expectancy <6 months.
- ⇒ Pregnancy.

ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; LVO, large vessel occlusion; MR-DWI, MR-diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; Tmax, time to maximum of the residue function; rtPA, recombinant tissue-type plasminogen activator.
*Obtained either from the patient, the patient's legal representative or an independent physician who was not involved in the study.

Endovascular treatment

The thrombectomy technique was chosen at the discretion of the interventionalist on an individual patient basis and comprised either the use of a stent retriever, direct thrombus aspiration or a combination of both methods. Angioplasty and stenting of the proximal internal carotid artery (ICA) were performed as needed.

Reperfusion grades were assessed according to the modified thrombolysis in cerebral infarction (TICI) classification.

EVT was performed under general anaesthesia in all patients according to our institutional protocol, and based on the findings of recent meta-analyses, which demonstrated that patients who undergo EVT under general anaesthesia have better recanalisation rates and outcomes than those treated with conscious sedation.[18–20]

Medical management was consistent with the recommendations published by the European Stroke Organization.[17]

Therapeutic hypothermia

Cooling devices

Several studies have used the RhinoChill cooling device (BrainCool) for induction of hypothermia in patients after cardiac arrest[21 22] and brain injury,[14] where it is described in detail. The RhinoChill system comprises three components: a control unit that is connected to an oxygen supply; a set of tubes with two nasal catheters and a 2L bottle that contains coolant (perfluorohexane, a chemically and biologically inert fluorocarbon). The 10 cm long nasal catheters are fully inserted through the nostrils and feature spray ports on the dorsal surface to distribute the coolant in the nasal cavity. Evaporation of the coolant absorbs heat from the tissue and rapidly cools the nasal cavity to ~2°C, whereby the large nasopharyngeal surface area and extensive adjacent vascularity (carotid arteries and cavernous sinus) mediate the direct conductive and indirect haematogenous cooling of the brain and body.

In the present study, we used an oesophageal temperature probe to monitor cooling, since the temperature measured in the lower oesophagus has been shown to correlate best with the brain temperature.[16]

The components of the RhinoChill device can be connected within 30–60 s, and the device is ready to use as soon as it has been switched on. Preparation of the RhinoChill-system was performed by the attending neurologist. Coolant delivery is maintained at a constant ratio of oxygen flow, such that the cooling level is controlled by setting the oxygen flow rate between 0 L/min and 60 L/min.

In previous studies, the RhinoChill device has so far only been used to induce hypothermia with a maximum duration of 60–90 min.[14–16 21 22] Furthermore, the device does not have an automated control feedback unit, which would allow the target temperature of 35°C to be kept constant and would allow a controlled rewarming. Therefore, the cooling technique was switched to a surface cooling method (BrainCool) with an automated control system to maintain the target temperature of 35°C for a total of 6 hours after recanalisation and to achieve controlled rewarming.

Cooling protocol

Directly following intubation for EVT, an oesophageal temperature probe (Mon-a-Therm, Covidien, Massachusetts) was placed transorally to continuously measure oesophageal temperature (distance from incisors to tip: 30–35 cm, confirmation of correct position in the lower oesophagus by X-ray during subsequent angiography). In addition, tympanic temperature (BraunThermoscan Pro6000, New York) was measured at predefined time points. Then, the RhinoChill nasal catheters were introduced into the nasal cavity. The RhinoChill system was switched on, and oxygen flow was gradually increased to 60L/min within 1 min. After 20–25 min, the empty coolant bottle was changed and oxygen flow was continued at 40L/min. The maximal total duration of RhinoChill use was set to 90 min. Nasopharyngeal cooling was halted if the target oesophageal temperature of 35°C was attained, and, if applicable, restarted when the temperature reincreased to over 35°C.

After thrombectomy, the patient was immediately transferred to the neurological Intensive Care Unit (ICU), where cooling was maintained by surface cooling (BrainCool) for a duration of 6-hour postrecanalisation (or at the end of the EVT procedure when recanalisation was unsuccessful).

Thereafter, patients were actively rewarmed at a rate of 0.2 °C/hour (7 hours) until the oesophageal temperature reached 36.5°C, after which the cooling device was removed.

During the entire cooling and rewarming period up to 36.0°C, all patients were intubated, mechanically ventilated, and sedated, showing no response to vocal or physical stimulation (Richmond Agitation Sedation Scale score = −5).

Analgetic and sedating medications included propofol (mean dosage: 104±47 mg/hour) and remifentanyl (mean dosage: 0.21±0.15 mg/hour) in all patients, and norepinephrine (mean dosage: 0.14±0.25 mg/hour) was used to maintain systolic blood pressure between 140–160 mm Hg during the EVT procedure, and 120–160 mm Hg after recanalisation; the target mean arterial pressure was >75–80 mmHg.

Imaging

According to institutional protocol, patients within the 6-hour time window underwent non-contrast CT and CT-angiography (CTA) as well as optional CT-perfusion (CTP) at admission, whereas patients admitted after 6 hour, or those who had an unknown time window, underwent CT, CTA and CTP (Somatom-Definition-Flash or Somatom-Definition-64AS; Siemens).

Within a post-thrombectomy period of 24±3 hours, a non-contrast CT was performed to determine the potential presence of intracerebral haemorrhage. Further cranial CT or MRI scanning was performed at day 3–7 at the discretion of the treating neurologist, to determine the final infarct volume prior to initiation of oral anticoagulation.

To determine an irreversible initial infarct core and penumbra, the fully automated volumetry approach VEOcore (VEObrain[23]) was used. Final infarct volume on MRI was measured using VEOcore with an apparent diffusion coefficient threshold of <620 $\times 10^{-6}$ mm^2/s for infarct determination. Final infarct volume on CT was measured by manually tracing the hypodense infarct area on each slice and multiplying the traced area with the slice thickness (Syngo.via, Siemens Healthcare).

Final infarct volumes were used to compute relative penumbra consumption, defined as ((final infarction volume-initial CTPcore)/initial CTPpenumbra) and were computed for each patient as previously described.[10]

Outcomes

Primary outcome

The primary outcome was the time taken to reach the oesophageal target temperature of 35°C from the point of initiation of transnasal cooling.

Secondary outcomes

Secondary outcome measures included the modified Rankin Scale (mRS) at both discharge and 3 months, the NIHSS at 24 hours and at discharge as well as the evolution of ischaemic core and penumbra from admission to day 2–7 after EVT.

Safety outcomes included all serious adverse events occurring within 48 hours of initiation of cooling. This involved all device-associated complications, disturbances of electrolytes and renal function, cardiac arrhythmia, haemodynamic instability, pneumonia, any intracranial bleeding and symptomatic intracranial haemorrhage within 48 hours as well as smell and taste disturbances at day 7 (Sniffin' sticks, burghart-Messtechnik, Holm, Germany).

Statistics

Variables were tested for normal distribution using the Shapiro-Wilk test. Given that not all data were distributed normally, variables are presented as the median and IQR of distribution. NIHSS scores (admission vs day 7), the initial and final infarct core volumes and differences between patients with good (mRS 0–2) and poor (mRS 3–6) 90-day outcome were compared, using the Wilcoxon test and Mann-Whitney-U-Test. Statistics were performed using the IBM SPSS-Statistics-software V.28.0.1.0.

RESULTS

Patient characteristics

A total of 22 patients (median age 77y, range 50–94) were enrolled from December 2021 until May 2022. The baseline characteristics are shown in table 1. The median NIHSS score at admission was 15 (12.5–19.75) and the ASPECTS score was 9 (8.25–10). The median time from LSN-to-admission was 265 min (191–490), and 14 patients (64%) received intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA). Nine patients (41%) were transferred from primary stroke centres after diagnosis of LVO.

Table 1 Patient characteristics (n=22)

Parameter	
Age (years)	77 (70–83) (range, 50–94)
Males	12 (55%)
Weight (kg)	75 (70–79)
Race and ethnicity	
Caucasian	22 (100%)
Premedication	
Aspirin	5 (23%)
Oral anticoagulants	6 (27%)
Statins	7 (32%)
Risk factors	
Hypertension	15 (68%)
Coronary heart disease	7 (32%)
Diabetes mellitus	5 (23%)
Current smoker	4 (18%)
Hyperlipidaemia	8 (36%)
Prior stroke	3 (14%)
Pre-morbid mRS	
0	12 (55%)
1	4 (18%)
2	6 (27%)
Reason for stroke	
Atrial fibrillation	11 (50%)
Patent foramen ovale	2 (9%)
Proximal ICA stenosis >50%	4 (18%)
Unknown	5 (23%)
Time LSN-to-admission (min)	265 (191–490)
NIHSS at admission	15 (12.5–19.75)
ASPECTS at admission	9 (8.25–10)
Initial perfusion imaging (n=20) (mL)	
Infarct core*	19 (6–38)
Penumbra†	103 (85–118)
rtPA given	14 (64%)

Data are presented as n (%), median (IQR).
*Infarct core: CBF<30% of contralateral normal tissue.
†Penumbra: volume difference between hypoperfused tissue (time to the maximum of the residue function (Tmax)>6s) and infarct core.
ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; LSN, last seen normal; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

EVT procedure

The characteristics of the EVT procedures are shown in table 2. The median time from LSN-to-groin-puncture and recanalisation was 309 min (228–580) and 355 min

Table 2 Characteristics of endovascular thrombectomy and hypothermia (n=22)

Parameters	
Occlusion site, n (%)	
First segment of MCA (M1)	12 (55%)
Second segment of MCA (M2)	3 (14%)
Distal ICA+M1	3 (14%)
Tandem occlusion (proximal ICA+M1)	4 (18%)
Left hemisphere	11 (50%)
Reperfusion, n (%)	
mTICI 3	9 (41%)
mTICI 2b	11 (50%)
mTICI 2a	0
mTICI 0 to 1	2 (9%)
Time point of EVT (min)	
LSN-to-groin (min)	309 (228–580)
<6 hour	11 (50%)
>6 hour	5 (23%)
Unknown	6 (27%)
LSN-to-recanalisation	355 (258–645)
Times from door to X: (min)	
Intubation	54 (34–75)
Start transnasal cooling	58 (39–79)
Groin puncture	65 (45–81)
Recanalisation	123 (93–140)
Transnasal cooling	
Time taken to reach 35°C (min)	30 (23–37)
Cooling rate (°C/hr)	2.6 (2.1–2.9)
Temperature at recanalisation	34.9 (34.7–35.0)
35°C at recanalisation (n)	19 (86%)
Temperature of patients who did not reach 35°C at by recanalisation (°C)	35.2, 35.2, 35.5
Hypothermia	
Duration of steady-state-hypothermia (h)	6.6 (6.3–6.9)
Duration of re-warming (h)	7 (7–9)

Data are presented as n (%), median (IQR).
ICA, internal carotid artery; LSN, last seen normal; MCA, middle cerebral artery; mTICI, modified thrombolysis in cerebral infarction.

(258–645), respectively. Eleven patients were admitted <6 hour after symptom onset, 5 patients >6 hour after onset and 6 patients had an unknown time window.

Twenty patients (91%) were treated with stent retrievers (Solitaire n=16, pReset n=2, Embotrap n=2), of which three additionally received direct aspiration, and two (9%) showed spontaneous recanalisation with angiographic demonstration. Four patients (18%) with tandem occlusion of the proximal ICA and the first segment of the middle cerebral artery received additional ICA-stenting. Successful recanalisation with TICI scores of 2b–3 was obtained in 19/22 patients (91%).

Hypothermia

Transnasal cooling was initiated 58 min (39–79) after admission, 5 min (4–5.25) after EVT-dependent intubation, and 5.5 min (2–10) prior to groin puncture (table 2).

The course of oesophageal and tympanic temperatures within the first 14 hours of hypothermia induction is shown in figure 1. The median oesophageal and tympanic temperature before the start of cooling (is equal to time 0 in figure 1) was 36.35°C (36.0–36.6) and 36.45°C (36.0–36.6), respectively.

The median time required from the start of RhinoChill to reach the oesophageal target temperature of 35°C was 30 min (23–37), with a cooling rate of 2.6°/hour (range, 1.5–3.6). Despite the interruption of transnasal cooling when the oesophageal target temperature of 35°C was reached, temperature continued to slowly decrease in all but 2 patients (time 45 and 60 min in figure 1). In these two patients, oesophageal temperature reincreased to over 35°C after cessation of transnasal cooling before recanalisation was achieved, and RhinoChill had to be restarted for a duration of 6 min and 8 min, respectively, to reach the target temperature of <35°C again.

The target temperature was reached in all patients (range 13–78 min) and was <35°C in 86% (19/22) of patients at the time of recanalisation. Median oesophageal temperature at recanalisation was 34.9°C (34.7–35.0).

Although no active cooling was carried out during the period between the end of thrombectomy in the angiography room and the arrival at the ICU (median duration 31 min (24–36)), oesophageal temperature continued to slowly decrease to 34.8°C (34.6–35.0). Thus, after arrival in the ICU, surface cooling was used to maintain stable hypothermia of 35°C for a duration of 5.6 hours (5.4–5.7), thus achieving a complete duration of hypothermia of 6 hours after recanalisation (figure 1). The median oesophageal temperature during the surface cooling period was 34.9°C (34.7–35.0).

The course of tympanic temperatures (figure 1B) did not differ significantly when compared with oesophageal temperatures but showed greater dispersion as indicated by wider IQR throughout.

The duration of rewarming was 7 hour (7–9), and patients were intubated for 21 hours (16–25).

Functional outcome

The median NIHSS score was 15 (12.5–19.75) at admission and decreased to 7 (3–12.5) at 24 hours, and 2 (1–8) at day 7 (p<0.001). The respective lengths of stay in the ICU and the hospital were 3 (2–4) and 8 (7–10) days. Nine patients (41%) were discharged home. The distribution of mRS at discharge (median day 8 (7–10)) and after 3 months (day 89, (86–92)) is shown in figure 2. A good neurological outcome with an mRS score of 0–2 was seen in 14 out of 22 patients (64%) at discharge, and in 15 patients (68%) after 3 months. Eleven patients

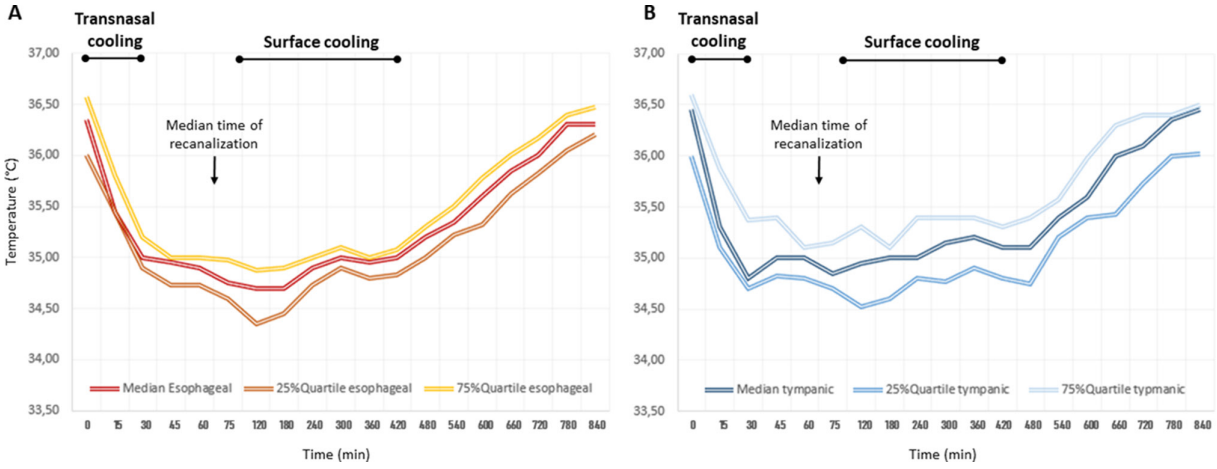

Figure 1 Oesophageal (A) and tympanic (B) temperatures in the first 14 hours of cooling induction. (A) After start of transnasal cooling (= time 0), oesophageal temperature decreased from 36.35°C at admission to target temperature of 35°C within 30 min. Despite halting transnasal cooling when target temperature of 35°C was reached, temperature continued to decrease slowly (time 45–60 min). At the time of recanalisation, median oesophageal temperature was 34.9°C. Between end of thrombectomy procedure and arrival to the ICU, temperature further decreased slowly without active cooling (time 75 min). Surface cooling was started 31 min after recanalisation on ICU for 5.6 hour to reach a total duration of steady-state hypothermia of 35°C for 6 hour after recanalisation. (B) Course of tympanic temperatures did not differ significantly when compared with oesophageal temperatures, although tympanic temperatures decreased faster during transnasal cooling and were slightly above the oesophageal values during surface cooling and rewarming phase.

(50%) had reached an excellent functional outcome by 3 months post-treatment, with an mRS score of 0–1. In the subgroup of patients who additionally received intravenous thrombolysis (n=14), 90-day outcome was good (mRS 0–2) in nine patients (71%).

Overall, patients with a good 90-day outcome had a significantly higher ASPECTS score at admission (10 (9.25–10) vs 8 (7.5–9), p<0.001) and a shorter ventilation time (18 hours (16–23) vs 38 hours (24–59), p=0.006) compared with patients with poor outcome. Furthermore, patients with good outcome were younger (74 years (69–82) vs 80 years (77–85)), were more often women (47% vs 43%), had lower NIHSS at admission (14 (11–17) vs 18.5 (14–20)) and received intravenous thrombolysis more often (67% vs 57%), although these differences did not reach significance.

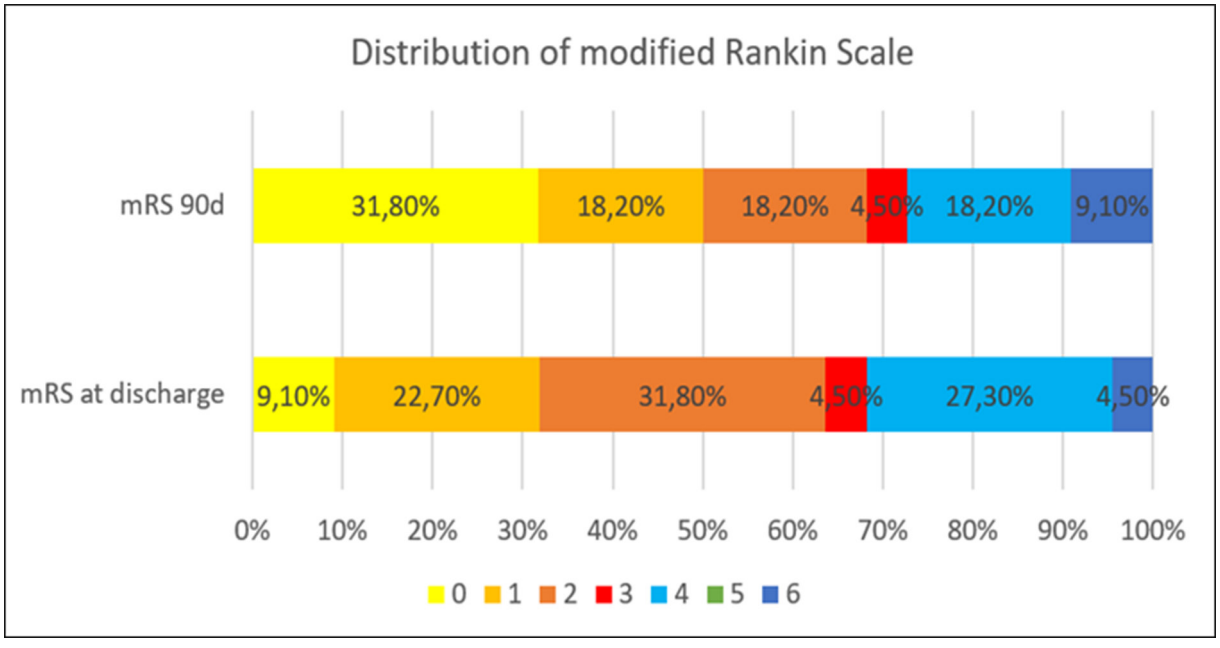

Figure 2 Distribution of modified Rankin Scale (mRS) score at discharge (median day 8) and after 3 months. A good neurological outcome with a mRS score of 0–2 was observed in 14 out of 22 patients (64%) at discharge, and in 15 patients (68%) after 3 months.

Table 3 Complications and physiological parameters during and after hypothermia

Bradycardia (37–39 bpm),* n (%)	7 (32%)
Pneumonia,† n (%)	4 (18%)
Haemorrhagic transformation‡ n (%)	4 (18%)
Symptomatic intracerebral haemorrhage,§ n	0
Nose bleeding,* n (%)	1 (5%)
Smell or taste disorder (day 7), n	0
Blood pressure,¶ mm Hg, (mean±SD)	
Systolic	136±12
Mean	86±8
At admission and at 24 hours	
Potassium (mmol/l)	4.2±0.4; 4.2±0.4
Sodium (mmol/l)	139±2 ; 140+3
Creatinine (mg/dl)	0.95±0.3; 0.87±0.25

*Without the need for intervention.
†Defined as any new pulmonary infiltrate on radiographic imaging occurring <48 hours after admission, combined with at least one of the subsequent findings: fever >38°C, leucopenia/leucocytosis, purulent secretions with positive cultures.
‡Asymptomatic, small or confluent petechiae within the infarcted area without space-occupying effect on CT, within 48 hours of cooling.
§Parenchymal haematoma type 2 on CT within 48 hours of cooling, defined as clots in at least 30% of the infarcted area, with a space-occupying effect in combination with worsening of NIHSS by >4 points.
¶Average reading of during the first 14 hours of cooling induction.
NIHSS, National Institutes of Health Stroke Scale.

Safety outcomes

Procedural and clinical complications are summarised in table 3. The most common side effect during hypothermia was asymptomatic bradycardia not requiring intervention (n=7, 32%). Pneumonia occurred in four (18%) patients. Asymptomatic haemorrhagic transformation on the 24-hour-CT was observed in four (18%) patients. None of the patients showed signs of symptomatic intracranial haemorrhage, disturbances in electrolytes, renal function, coagulation or smell or taste function.

In the subgroup of patients receiving additional intravenous thrombolysis (n=14), asymptomatic haemorrhagic transformation occurred in three patients (21%), and nose bleeding (without the need for intervention) in one patient (7%).

The hospital mortality and 3-month mortality rates were 5% (1/22; withdrawal of care due to a persistent, severe deficit in an 88-year-old patient at day 4) and 9% (2/22; death due to myocardial infarction and multiorgan failure 6 weeks poststroke onset in the rehabilitation hospital), respectively.

Evolution of infarct core and penumbra

VeoCore analysis of initial infarct core and penumbra volumes could be performed in 20 patients (CTP was done in 11 patients with unknown or >6-hour time window and (optionally) in 9 of 11 patients within the 6-hour time window). The initial infarct core volume (19 mL (6–38)) and infarct core on day 2–7 (22.5 mL (8.5–31)) did not differ significantly (p=0.379; final infarct volume was defined by the 24-hour CT in six patients, by CT at day 3–7 in four patients, and by MRI at day 2–7 in 10 patients). The volume of penumbra tissue at risk was 103 mL (85–118) at admission. Relative penumbra consumption was 5% (0–8), meaning that 95% (90–100) of the initial penumbra could be salvaged.

DISCUSSION

This pilot study has demonstrated the feasibility and safety of a new cooling algorithm that covers the prerecanalisation and postrecanalisation phase in thrombectomy patients. This hypothermia-based approach was associated with very good short and 90-day functional outcomes.

Although hypothermia has consistently been associated with robust neuroprotection in preclinical studies, all randomised-controlled trials in acute ischaemic stroke patients have failed to confirm the potential benefits of cooling.[6 7] The reasons for this are manifold and include the following major problems: (1) the delay in the initiation of the cooling procedure due to either study protocol limitations, or invasive and time-consuming cooling methods; (2) the difficulty and infeasibility of reaching and then maintaining the target temperature in awake patients due to intolerance and shivering[8]; (3) the heterogeneity of the patient cohort,[7] which usually comprises patients with different stroke severities and can also include those with mild and lacunar stroke, these latter having a small amount of tissue-at-risk; (4) low recanalisation rates of 10%–30%, even in patients receiving rtPA[6 7 24] and (5) poor recruitment due to the elaborate and difficult cooling procedures.[8]

The recent success of thrombectomy in patients with LVO combined with the high proportion of tissue-at-risk and high recanalisation rates in these patients offers new perspectives for the use of hypothermia in acute stroke patients. Consequently, we attempted to address the above-described reasons for hypothermia failure by designing a hypothermia protocol that differed from previous trial protocols in the following five main aspects:

1. The technique is relatively simple and minimally-invasive, effective means of quickly inducing hypothermia.
2. Hypothermia was initiated prior to recanalisation in order to modulate reperfusion injury.
3. Study inclusion was restricted to patients with LVO and EVT with high recanalisation rates and significant penumbra, which is the main target of neuroprotection.

4. Patient discomfort, shivering and ultimate cessation of the cooling procedure, was avoided by extending peri-interventional intubation and sedation throughout the entire period of cooling and rewarming.
5. A very mild degree of hypothermia (35°C) was applied for a relatively short period of time to minimise side effects, while still possibly offering a certain degree of neuroprotection during the most vulnerable prerecanalisation and early postreperfusion phases.

Patient selection for hypothermia

The use of hypothermia as a potent neuroprotective agent is aimed at protecting and preserving the ischaemic penumbra. Therefore, the appropriate selection of patients that can benefit from such a therapeutic strategy is essential. However, most clinical trials on hypothermia included a heterogenous patient collective with different stroke severities, and recanalisation could not be achieved in a significant proportion of participants.[6 7] Therefore, in the present study, patients were only included if they had an LVO with an indication for thrombectomy (according to present European guidelines). All patients were intubated for EVT according to our established institutional protocol that is based on recent meta-analyses,[18–20] and ventilation and sedation were continued for the entire period of hypothermia and rewarming. By using this regimen, only intubated and sedated patients with an assumed large volume of tissue-at-risk were included in the study. Thereby, no direct side effects of hypothermia such as shivering and intolerance were observed, which is otherwise often the case in stroke patients who are awake. Furthermore, the immediate initiation and maintenance of hypothermia was feasible in all patients. As a consequence, the target temperature of 35°C was achieved in all patients and maintenance of the target temperature as well as a steady rise in temperature during rewarming was ensured, without significant fluctuations.

In addition, by exclusively including thrombectomy patients, the vast majority of patients (91%) were successfully recanalised. Preclinical studies consistently showed strong effects of neuroprotection using hypothermia in reperfusion models, but the effects observed in permanent occlusion models were less robust,[6 25] suggesting that recanalisation and reperfusion are mandatory for hypothermia to be beneficial.

Timing of hypothermia

In the cerebral ischaemia that follows LVO, the infarct core rapidly grows over time, so that any therapeutic measures that aim to protect the tissue-at-risk need to be initiated as soon as possible. Due to the hypothermia induction methods used in previous studies, the potential beneficial effects of cooling were additionally impaired by the slow-acting treatment methods that ensued. In contrast, RhinoChill is an easy to use transnasal cooling device, which allows the cooling process to be started within just a few minutes.

Using this device, cooling could already be initiated just 5 min after EVT-dependent intubation and never took more than 1 hour postadmission. The target temperature of 35°C was reached after a median of 30 min. Importantly, since the RhinoChill preparation took place simultaneously to the patient preparation for angiography, no time delay in groin puncture for EVT occurred.

Thus, with this approach, a fast induction of hypothermia was feasible. This is important, given that preclinical studies have demonstrated the greater protective effects conferred by prompt intraischaemic hypothermia compared with delayed intraischaemic or postischaemic hypothermia.[6 26] By reducing the energy demand of the tissue, hypothermia can limit ischaemic core growth and prevent the penumbra from evolving into an infarction.[27]

Duration and depth of hypothermia

The ideal extent and duration of hypothermia in acute ischaemic stroke patients are yet to be established, whereas one meta-analysis of preclinical studies found a significant association between lower temperatures and a more prominent reduction in infarct volume,[25] a more recent meta-analysis did not find any hypothermic depth level to be particularly superior to the others.[28]

With respect to hypothermia duration, several experimental findings have suggested that a longer cooling period might provide better neuroprotection.[6] However, a recent study using both cell culture and animal stroke models found that a shorter bout of therapeutic hypothermia may be superior and suggested that hypothermia at either 33°C and 35°C effectively preserves all neuronal cell types.[29]

In addition, prolonged application and lower temperature targets of hypothermia significantly increase the risk of side effects, especially cardiovascular complications and infections, which may weaken or even offset the protective effects of cooling.[6 30] Thus, the optimal conditions need to be carefully titrated in order to maximise efficacy while minimising complications.

In summary, the most recent preclinical findings from animal and cell culture models suggest that fast,[31] mild (34–35°C[29]) and non-prolonged[29] application of hypothermia can potentially provide the best long-term neuroprotective effects.

Accordingly, we used RhinoChill for a fast initiation of cooling down to the level of mild (35°C) hypothermia in the angiography room before recanalisation and continued hypothermia with surface cooling for a relatively short period of 6-hour postrecanalisation. This coincided with the most vulnerable reperfusion phase within the first hours of recanalisation, while minimising the risk of side effects.

Indeed, the present findings support this new cooling protocol, since 68% of patients gained independency after 3 months, even though 50% of patients had a time window that was either greater than 6 hour or unknown altogether, and 41% were transferred from primary stroke centres. This proportion of patients with a good neurological

outcome is superior to that observed in randomised trials with normothermic thrombectomy patients (mean 46%[1]) as well as to findings from previous studies from our own institution (32%–42%[32 33]). However, since there was no control group in the present study, we cannot exclude that the good outcome and penumbra salvage observed in this study could reflect the brain tissue saved solely due to timely and successful EVT procedure.

Side effects of hypothermia

The most common side effect in the present study was asymptomatic bradycardia (32% of patients), which was observed during hypothermia but did not need intervention and spontaneously disappeared after rewarming. No other complications that have been described in previous studies on hypothermia in acute stroke were observed. Of note, none of the patients suffered from symptomatic intracranial bleeding despite additional thrombolysis in 64% and ICA stenting, which required additional antiplatelet therapy in 18% of patients.

The pneumonia rate of 18% in the present study is comparable to that reported in prospective trials with normothermic EVT patients under general anaesthesia, with a mean pneumonia rate of 19.4% (range: 13.3%–46%[18 20]).

Importantly, the median intubation time was 21 hours, which is clearly longer than that usually observed in normothermic EVT patients. However, in the present study, we did not observe any discomfort and shivering representative of physiological reactions that increase metabolic rate, oxygen consumption and respiratory burden. These side effects would obviously be unfavourable for patients with an acute stroke.[34] Moreover, the relatively long intubation time was not associated with an increase in complications such as pneumonia rate.

CONCLUSION

This pilot study has demonstrated the feasibility of a novel cooling approach in thrombectomy patients, whereby no symptomatic complications and a very good 90-day outcome were observed. The multicentre randomised controlled COmbination of Targeted temperature management and Thrombectomy after acute Ischemic Stroke-2 trial (COTTIS-2) will evaluate the efficacy of this approach and is planned for 2023 (supported by the EU).

Acknowledgements We acknowledge support by the Open Access Publication Fund of the University of Freiburg.

Contributors JB (responsible for the overall content as the guarantor): ethics proposal and study protocol writing, patient enrolment and care, data analysis, manuscript writing, statistics, manuscript co-writing, imaging analysis. RK: study protocol writing, statistics, manuscript co-writing. FA-R: ethics proposal co-writing, data analysis, manuscript co-writing. JL: patient enrolment, data analysis, manuscript co-writing, imaging analysis. MF: study protocol co-writing, data analysis, statistics, manuscript co-writing CT: patient care, data analysis, manuscript co-writing, imaging analysis. W-DN: ethics proposal and study protocol writing, patient enrolment, data analysis, manuscript writing, statistics.

Funding JB got his salary paid in part through the EU project Horizon-2020, project Acronym CUCUMBER; project number 958809.

Competing interests MF is an employee of the company BrainCool.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institutional Ethics Committee of the University of Freiburg; ID 21-1054. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs

Jürgen Bardutzky http://orcid.org/0000-0003-3372-2651
Johann Lambeck http://orcid.org/0000-0002-4078-778X

REFERENCES

1 Goyal M, Menon BK, van Zwam WH, *et al*. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723–31.
2 Badhiwala JH, Nassiri F, Alhazzani W, *et al*. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA* 2015;314:1832–43.
3 Haussen DC, Nogueira RG, Elhammady MS, *et al*. Infarct growth despite full reperfusion in endovascular therapy for acute ischemic stroke. *J NeuroInterv Surg* 2016;8:117–21.
4 Al-Mufti F, Amuluru K, Roth W, *et al*. Cerebral ischemic reperfusion injury following recanalization of large vessel occlusions. *Neurosurgery* 2018;82:781–9.
5 Kurisu K, Yenari MA. Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise. *Neuropharmacology* 2018;134:302–9.
6 Wu D, Chen J, Hussain M, *et al*. Selective intra-arterial brain cooling improves long-term outcomes in a non-human primate model of embolic stroke: efficacy depending on reperfusion status. *J Cereb Blood Flow Metab* 2020;40:1415–26.
7 Kuczynski AM, Marzoughi S, Al Sultan AS, *et al*. Therapeutic hypothermia in acute ischemic stroke-a systematic review and meta-analysis. *Curr Neurol Neurosci Rep* 2020;20:13.
8 van der Worp HB, Macleod MR, Bath PM, *et al*. Therapeutic hypothermia for acute ischaemic stroke. results of a European multicentre, randomised, phase III clinical trial. *Eur Stroke J* 2019;4:254–62.
9 Chamorro Á, Dirnagl U, Urra X, *et al*. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol* 2016;15:869–81.
10 Dehkharghani S, Fleischer CC, Qiu D, *et al*. Cerebral temperature dysregulation: MR thermographic monitoring in a nonhuman primate study of acute ischemic stroke. *AJNR Am J Neuroradiol* 2017;38:712–20.
11 Dehkharghani S, Yaghi S, Bowen MT, *et al*. Mild fever as a catalyst for consumption of the ischaemic Penumbra despite endovascular reperfusion. *Brain Commun* 2020;2:fcaa116.
12 Diprose WK, Liem B, Wang MTM, *et al*. Impact of body temperature before and after endovascular thrombectomy for large vessel occlusion stroke. *Stroke* 2020;51:1218–25.
13 Wu C, Zhao W, An H, *et al*. Safety, feasibility, and potential efficacy of Intraarterial selective cooling infusion for stroke patients treated with mechanical thrombectomy. *J Cereb Blood Flow Metab* 2018;38:2251–60.
14 Abou-Chebl A, Sung G, Barbut D, *et al*. Local brain temperature reduction through intranasal cooling with the RhinoChill device: preliminary safety data in brain-injured patients. *Stroke* 2011;42:2164–9.
15 Wolfson MR, Malone DJ, Wu J, *et al*. Intranasal perfluorochemical spray for preferential brain cooling in sheep. *Neurocrit Care* 2008;8:437–47.
16 Poli S, Purrucker J, Priglinger M, *et al*. Rapid induction of cooling in stroke patients (iCOOL1): a randomised pilot study comparing cold infusions with nasopharyngeal cooling. *Crit Care* 2014;18:582.
17 Turc G, Bhogal P, Fischer U, *et al*. European stroke Organisation (ESO) - European society for minimally invasive neurological therapy

(ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg* 2023;15:e8.
18 Bai X, Zhang X, Wang T, *et al*. General anesthesia versus conscious sedation for endovascular therapy in acute ischemic stroke: a systematic review and meta-analysis. *J Clin Neurosci* 2021;86:10–7.
19 Campbell D, Diprose WK, Deng C, *et al*. General anesthesia versus conscious sedation in endovascular thrombectomy for stroke: a meta-analysis of 4 randomized controlled trials. *J Neurosurg Anesthesiol* 2021;33:21–7.
20 Lee C-W, Chang Y-P, Huang Y-T, *et al*. General anesthesia but not conscious sedation improves functional outcome in patients receiving endovascular thrombectomy for acute ischemic stroke: a meta-analysis of randomized clinical trials and trial sequence analysis. *Front Neurol* 2022;13:1017098.
21 Castrén M, Nordberg P, Svensson L, *et al*. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: pre-ROSC intranasal cooling effectiveness). *Circulation* 2010;122:729–36.
22 Busch H-J, Eichwede F, Födisch M, *et al*. Safety and feasibility of Nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest. *Resuscitation* 2010;81:943–9.
23 Kellner E, Reisert M, Kiselev VG, *et al*. Automated infarct core volumetry within the hypoperfused tissue: technical implementation and evaluation. *J Comput Assist Tomogr* 2017;41:515–20.
24 Bhatia R, Hill MD, Shobha N, *et al*. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke* 2010;41:2254–8.
25 van der Worp HB, Sena ES, Donnan GA, *et al*. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain* 2007;130:3063–74.
26 Krieger DW, Yenari MA. Therapeutic hypothermia for acute ischemic stroke: what do laboratory studies teach us? *Stroke* 2004;35:1482–9.
27 Heiss WD. Malignant MCA infarction: pathophysiology and imaging for early diagnosis and management decisions. *Cerebrovasc Dis* 2016;41:1–7.
28 Dumitrascu OM, Lamb J, Lyden PD. Still cooling after all these years: meta-analysis of pre-clinical trials of therapeutic hypothermia for acute ischemic stroke. *J Cereb Blood Flow Metab* 2016;36:1157–64.
29 Lyden PD, Lamb J, Kothari S, *et al*. Differential effects of hypothermia on neurovascular unit determine protective or toxic results: toward optimized therapeutic hypothermia. *J Cereb Blood Flow Metab* 2019;39:1693–709.
30 Al-Senani FM, Graffagnino C, Grotta JC, *et al*. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the coolgard system and icy catheter following cardiac arrest. *Resuscitation* 2004;62:143–50.
31 Zhao J, Mu H, Liu L, *et al*. Transient selective brain cooling confers neurovascular and functional protection from acute to chronic stages of ischemia/reperfusion brain injury. *J Cereb Blood Flow Metab* 2019;39:1215–31.
32 Fuhrer H, Forner L, Pruellage P, *et al*. Long-term outcome changes after mechanical thrombectomy for anterior circulation acute ischemic stroke. *J Neurol* 2020;267:1026–34.
33 Taschner CA, Trinks A, Bardutzky J, *et al*. Drip-and-ship for thrombectomy treatment in patients with acute ischemic stroke leads to inferior clinical outcomes in a stroke network covering vast rural areas compared to direct admission to a comprehensive stroke center. *Front Neurol* 2021;12:743151.
34 Polderman KH, Herold I. Therapeutic hypothermia and controlled Normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 2009;37:1101–20.
35 Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708–18.
36 Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.