Selective retrograde cerebral cooling in complete cerebral circulatory arrest

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Abstract:
BACKGROUND AND PURPOSE: Cerebral hypothermia is a known neuroprotectant with promising applications in the treatment of ischemic events. Although systemic cooling is standard in post-cardiac arrest care, the deleterious effects of whole-body cooling have precluded it from translation into a viable treatment option for acute ischemic stroke (AIS). Selective cerebral cooling has been proposed as a method to minimize these risks while granting the neuroprotection of therapeutic hypothermia in AIS.

METHODS: In a porcine model (n = 3), the efficacy of selective retrograde cerebral cooling through the internal jugular vein was evaluated in the setting of complete cerebral circulatory arrest. Furthermore, a novel endovascular device and cooling system enabling selective retrograde cerebral cooling were studied in a normothermic perfused cadaver.

RESULTS AND CONCLUSION: Neurologic assessment of animals receiving this therapy reflected substantial neuroprotection in animals undergoing both 15 min and 30 min of otherwise catastrophic complete cerebral circulatory arrest. The novel endovascular device and cooling system were validated in human anatomy, demonstrating successful cerebral cooling, and feasibility of this mechanism of selective retrograde cerebral cooling.

Keywords: Retrograde cooling, selective cooling, targeted hypothermia

Introduction

Despite the remarkable advancement in large vessel occlusion (LVO) stroke care that has come from the widespread use of mechanical thrombectomy following overwhelmingly efficacious trial results,[1] there remains ample room for improvement in patient outcomes. Standard therapy in the management of acute ischemic stroke (AIS) includes intravenous thrombolytic, recombinant tissue plasminogen activator (rtPA), to break up clots, and endovascular mechanical thrombectomy, to physically remove clots,[2] with the joint goal of recanalization. Only an estimated 2%–5% of all AIS patients in the US receive rtPA due to eligibility limitations[3] including presentation beyond 4.5 h of symptom onset[2] and contraindications.[4] Furthermore, just 10% of AIS patients may be considered eligible for thrombectomy, with eligibility defined as the presence of mechanically accessible clot based on location, low risk of reperfusion injury after removal, and sufficient penumbral brain tissue to be spared with recanalization.[2,5,6] Although the population receiving thrombectomy is expected to grow with expanding eligibility criteria,[7] poor functional outcomes remain a reality for the majority of AIS patients receiving the gold standard of care. Despite best practices, negative functional outcomes for AIS patients treated with thrombectomy, defined by a modified Rankin Score (mRS) at 90 days of 3 to 6 indicating moderate-to-severe disability or death, is experienced by 54% of patients.[1,8]
Similarly, 50.4% of AIS patients receiving rtPA experience a negative functional outcome. Cerebral cooling, a therapeutic strategy with demonstrable neuroprotective benefits through a myriad of mechanisms, has been proposed as an adjunct treatment in the management of AIS. In this proof of concept study, we assess the efficacy of an endovascular approach for rapid selective cerebral cooling through the internal jugular vein in a porcine model of complete cerebral circulatory arrest. In addition, we present insights from a feasibility study performed in a normothermic perfused human cadaver using a novel endovascular device.

**Methods**

**Cerebral circulatory arrest in porcine model**

Three yorkshire pigs (53.9 ± 4.4 kg) were studied. Following induction of anesthesia, monitoring apparatus were placed, with cerebral and body temperatures measured by nasopharyngeal and rectal probes, respectively. The right internal jugular vein was cannulated in a retrograde fashion with a 14-gauge catheter and ligated proximally.

Infusion of 0°C–2°C normal saline was initiated retrograde through the internal jugular vein catheter cephalad to the location of vein ligation. Infusion of cooled saline was administered using a pressure bag set to and manually maintained at 300 mmHg, for an approximate rate of 250 cc/min.

Following infusion of 1 L of cooled saline, complete circulatory arrest was initiated for 15 min, 30 min, and 90 min as an infusion of cooled saline continued. The 90-min animal served to confirm that the technique used for complete circulatory arrest was indeed causative of ischemic brain damage and to provide an upper bound of arrest duration for which therapeutic cooling may not provide benefit, as established by the hypothermic circulatory arrest human data of McCullough et al. 1999.

Complete circulatory arrest was established with placement of bulldog clamps on the innominate artery, left subclavian artery, distal subclavian arteries bilaterally, and the internal thoracic arteries just distal to the anastomosis with the subclavian artery as described in Allen et al. 2012.

The administration of cooled saline was limited to 4–6 L per animal. After the allotted duration of complete circulatory arrest time was achieved, cerebral perfusion was restored, and the animals were rewarmed to physiologic temperatures prior to extubation.

The extent of neurologic dysfunction was measured at 4 and 24 h postextubation using a Neurological Deficit Score (NDS). NDS evaluates neurologic status on a scale of 0–500, with 0 representing normal function, using categories including level of consciousness, respiration, cranial nerve function, motor and sensory function, and behavior. Animals were survived up to 36 h before sacrifice, necropsy, and histopathological analysis. The histological analysis included hematoxylin and eosin, and 1% 2,3,5-triphenyltetrazolium chloride (TTC) staining of the brain.

**Normothermic perfused cadaver**

An adult human cadaver was placed on an extracorporeal pump using 38°C–40.6°C simulated blood (Maximum Fidelity Surgical Simulations) to establish a pulsatile flow to replicate the thermodynamic conditions of a living body. The cadaver was brought to normothermia through perfusion and surface warming, with intramuscular, and bilateral intraparenchymal temperature probes reading 37°C–38°C. The novel device, a 9Fr intravascular catheter with a dedicated lumen for delivery of cooled fluids, was placed using the Seldinger technique, under ultrasound guidance, into the internal jugular vein.

In opposition to the continued flow of normothermic simulated blood, a 4°C–5°C simulated blood and normal saline mixture was pumped at a flow rate of 260 ml/min, through the intravascular device, retrograde through the internal jugular vein. Within 13 min, left and right intraparenchymal temperatures dropped to 18°C and 21°C, respectively.

**Results**

**Cerebral circulatory arrest in porcine model**

In the animal experiencing 15 min of complete cerebral circulatory arrest, brain temperature reached 29.3°C from 37.6°C following administration of 4 L of cooled saline over 20 min. Functionally, the animal was eating, drinking, and walking independently at 24 h postextubation, with an NDS of 26 indicating normal neurologic status.

The functional outcomes at 24 h for the animal undergoing 30 min of complete cerebral circulatory arrest were improved from the 15-min animal, with an NDS of 10. In this animal, 6 L of cooled normal saline were infused, and cerebral cooling from 36.8°C to 31.2°C was achieved.

The final animal experienced 90 min of complete cerebral circulatory arrest and was cooled to 25.4°C from 37.4°C. Postprocedure, the animal experienced seizures, with a 24 h NDS of 290, did not regain consciousness and was euthanized. The rectal temperature did not drop below 31.5°C in all animals [Table 1].
Normothermic control data were adapted from the literature following a similar protocol; a porcine model ($n = 4$) undergoing 30 min of complete cerebral circulatory arrest without cooling resulted in a mean historical NDS score of $241 \pm 40$ at 24 h.$^{[11]}$

In the 15 min and 30 min complete circulatory arrest animals, no indication of neuronal necrosis was seen [Figure 1a and b], and no gross evidence of cell death was apparent on TTC staining [Figure 2a]. In the animal undergoing 90 min of complete circulatory arrest, microscopic changes of laminar cortical necrosis indicative of hypoxic-ischemic encephalopathy, cerebral necrosis, and moderate meningitis were noted [Figure 1c], in addition to gross evidence of necrosis by TTC staining [Figure 2b]. In all of the animals, mean arterial blood pressure, vena cava pressure, heart rhythm, and oxygen saturation remained normal over the course of the experiment.

**Normothermic perfused cadaver**

Intravascular cooling through the internal jugular vein of the cadaver resulted in a reduction of cerebral temperature by intraparenchymal probe of 19°C in 11 min, to a depth of 18°C. Cooled simulated blood flowed from the site of administration in the right internal jugular vein to the contralateral jugular vein, as confirmed on fluoroscopy, through the dural sinus [Figure 3]. The dural, transverse, sigmoid, superior sagittal, and petrosal sinuses as well as the facial vein were filled along this flow path.

**Table 1: Neurological Deficit Score scores at 4 and 24 h for animals undergoing 15 and 30 min of cerebral circulatory arrest with selective cerebral hypothermia, and control animals undergoing 90 min of arrest or 30 min without cooling**

| Experimental model | Depth of cerebral cooling | Depth of body cooling* | NDS score (0 normal - 500 death) | Status |
|--------------------|--------------------------|------------------------|---------------------------------|--------|
| Cerebral circulatory arrest, with cooling (min) | | | | |
| 15 min | 29.3°C | 35.0°C | Sedated | 26 | Eating, drinking, walking |
| 30 min | 31.2°C | 32.0°C | 66 | 10 | Eating, drinking, walking |
| 90 min | 25.4°C | 31.5°C | 215 | 290 | Seizures, no regain of consciousness |
| Historical control | | | | |
| 30 min, no cooling$^{[31]}$ | NA | NA | 243 | 241 | Seizures, no regain of consciousness |

*Body temperature measured by rectal temperature probe, †Nasopharyngeal probe placement too shallow for accurate measurement. NDS: Neurological Deficit Score, NA: Not available.

Therapeutic hypothermia in the setting of cardiac surgery dates back to the 1950s when de Bakey completed the first aortic arch aneurysm repairs.$^{[20,21]}$ Aortic arch operations had previously been deemed impossible as they would require interruption of blood flow to the aortic head vessels, resulting in transient global cerebral ischemia.$^{[22]}$ Cooling the brain provided a neuroprotective window during surgically induced global cerebral ischemia, allowing time for aneurysmal repair. Several groups have further validated cerebral cooling as an effective neuroprotectant in aortic arch surgery.$^{[22‑24]}$ Retrograde cerebral perfusion, a technique in which cooled blood is delivered through large veins in the opposite direction to normal venous blood flow, is commonly used in cardiac surgery to establish cerebral hypothermia.$^{[25]}$ Despite up to 1 h of interrupted blood flow to the brain, elective aortic arch replacement is associated with a 3% risk of brain damage.$^{[26]}$ In contrast, up to 54% of stroke patients are no longer functionally independent due to brain damage sustained even after receiving a thrombectomy.$^{[1]}$ These data further underscore the urgent need for the evaluation of novel methods for providing therapeutic hypothermia for neuroprotection in patients with AIS.

In addition, systemic therapeutic hypothermia of 32–36°C is recommended in post-cardiac arrest care by
the International Liaison Committee on Resuscitation guidelines.\[27\] The optimal temperature for targeted temperature management (TTM) in post-cardiac arrest care has been debated, with some studies suggesting no additional benefit with cooling to 33°C compared to 36°C.\[28\] and others displaying improved outcome in patients recovering from arrest with nonshockable rhythm cooled to 33°C.\[29\] Additional studies in intra-arrest cooling have noted trends toward improvement in cardiac arrest patients with ventricular fibrillation.\[30\] Currently, both endovascular and surface\[31\] cooling techniques for TTM in cardiac arrest patients use systemic cooling. Systemic cooling, despite its possible neurologic benefits, has been associated with negative effects including increased pneumonia risk in post-cardiac arrest patients.\[32\] It is plausible that the selective cooling of the brain may confer the known neuroprotective benefits of therapeutic hypothermia while minimizing the detrimental effects of systemic cooling.

**Barriers to cooling in acute ischemic stroke**

Bringing therapeutic hypothermia to AIS patients has faced challenges due to a focus on systemic rather than selective cerebral cooling. A number of clinical trials were designed to investigate whether systemic cooling to 32°C–34°C, as implemented in post-cardiac arrest treatment, may benefit AIS patients.\[27,33–35\] Although both surface (The Copenhagen Stroke Study, COOL AID)\[35\] and endovascular methods of cooling (ICTuS, ICTuS-2)\[36,37\] established the feasibility of systemic therapeutic hypothermia in the setting of AIS, there were salient risks. Systemic cooling is associated with an increased risk of pneumonia, counterproductive shivering necessitating pharmacologic intervention, and major complications including pulmonary edema, decreased cardiac output, bradycardia, ventricular arrhythmias, asystole, and coagulopathy.\[13,38–40\] Conversely, selective cerebral hypothermia may offer neuroprotection without the associated risks of systemic cooling, and allows for
deeper hypothermia, to levels known to be protective in aortic arch surgery (≤ 28°C). [24]

**Animal models of selective cerebral cooling in acute ischemic stroke**

Selective cerebral cooling has shown neuroprotective efficacy in large animal models of AIS. [41-46] Reduction in infarct size as a result of selective cerebral cooling has been demonstrated in numerous animal stroke models. In a meta-analysis of 101 publications providing data on 3,353 animals, hypothermia reduced infarct size by 44%, with deeper cooling (≤31°C) associated with more dramatic reductions (30% at 35°C vs. >50% at 31°C). [47] In a rodent model, selective cerebral hypothermia achieved through endovascular cold saline flush prior to revascularization in MCA occlusion resulted in 65%-90% reduction in infarct volumes. [19,48,49] In a model of AIS, four baboons underwent selective brain hypothermia to 27°C for 12 h, following simulated LVO with subsequent thrombectomy and reperfusion. [42] Baboons in the experimental arm displayed a significantly reduced infarction volume (0.5 ± 1% of the ipsilateral cerebral hemisphere) compared to the four in the control group (35.4 ± 4.4%). [42] Importantly, in addition to a reduction in infarct size, cardiovascular derangement, pneumonia, or pulmonary edema did not occur in these animals. [36,37,50]

**Cerebral cooling in humans**

Furthermore, selective cerebral cooling methods have displayed efficacy in humans. [51,52] Intravascular infusion of cold saline presents one mechanism for selective brain cooling. [18] Intra-arterial delivery of 4°C saline into the ischemic territory in patients undergoing mechanical thrombectomy for LVO (n = 45) was associated with an mRS of 0 to 2 at 90 days in 51.1% of this population. [50] In contrast, 41.2% of patients in the control group undergoing thrombectomy without cooling (n = 68) were seen to have an mRS of 0 to 2 at 90 days, suggesting a trend toward an improved rate of functional independence with selective cerebral cooling. [53]

**Novel intravascular approach for selective retrograde cerebral cooling**

In this study, a novel approach was proposed and evaluated to establish selective retrograde cerebral cooling. The approach consists of occluding, unilaterally, the internal jugular vein, and administering cold fluid cephalad to the region of occlusion, for targeted brain cooling. The perfusate circulates the venous sinuses before exiting the intracranial space through the contralateral internal jugular vein. Our normothermic perfused cadaver study utilized a novel intravascular device facilitating this approach, and demonstrated that the flow of cooled perfusate outlets through the contralateral internal jugular vein. The contralateral internal jugular vein serving as a large vessel venous outflow path potentially mitigates the risk of venous congestion and cerebral edema. Such complications are known from cases of prolonged retrograde cerebral perfusion in cardiac surgery in which no large vessel venous outlet is available for perfusate; an efficient outlet for perfusate, as seen in our approach, may mitigate this risk.

**Discussion of Results**

In our study of cerebral circulatory arrest in a porcine model, selective cerebral cooling to <30°C by retrograde internal jugular infusion conferred significant neuroprotection in the setting of otherwise catastrophic complete cerebral circulatory arrest. In the animal undergoing 15 min of cerebral circulatory arrest, cerebral cooling to 29.3°C by nasopharyngeal probe was achieved. The depth of cerebral cooling reached in the animal undergoing 30 min of arrest, was not adequately assessed due to shallow nasopharyngeal probe placement, discovered on fluoroscopy, reaching 31.2°C [Table 1]. It can be inferred from the administration of a larger volume of saline (6 L vs. 4 L), and the resulting lower rectal temperature (32°C vs. 35°C) in the 30-min versus 15-min animal, that brain temperature in the 30-min arrest animal was ≤29.3°C [Table 1]. In animals experiencing 15 and 30 min of interrupted blood flow to the brain, an NDS of 26 and 10, respectively, at 24 h were demonstrated following retrograde infusion of cooled saline, compared to 241 in the historical control group. [11] The histopathological analysis further confirmed that cerebral cooling is associated with an avoidance of gross ischemic damage despite prolonged ischemic events as displayed in up to 30 minutes of complete cerebral circulatory arrest.

Our study of a normothermic perfused human cadaver demonstrates that retrograde cerebral perfusion for targeted brain cooling through a percutaneously placed intravenous catheter within the internal jugular vein is indeed feasible. Additionally, the notable speed (1.73°C/min in the cadaver versus 0.42°C/min in the 15-min circulatory arrest porcine model) and depth of cooling (18°C in the cadaver versus 25.4°C in the porcine model) exceed those seen in porcine models with similar device flow rates. Although a living model is superior for its incorporation of metabolic heat generation among other factors, the results suggest that cooling through the human vasculature, notably the dural venous sinus system and larger human internal jugular vein, may confer a more expedient route to deeper levels of hypothermia.
In our study of complete cerebral circulatory arrest, the neuroprotective effect of selective cerebral cooling using retrograde infusion of cooled fluid has been displayed. In this porcine model, cooling was initiated prior to cerebral circulatory arrest to demonstrate the efficacy of cooling against a normal cardiac output. Further studies are warranted to explore the role of retrograde selective cerebral cooling initiated after the restoration of blood flow to assess applicability in post-cardiac arrest and stroke care. Cooling initiated after simulated thrombectomy may yield particularly beneficial data regarding selective hypothermia as an adjunct to recanalization. In addition, the optimal depth and duration of selective cooling for neuroprotection in the setting of stroke have yet to be determined. Future studies exploring the effects of selective cooling on patient-relevant metrics such as ischemic volume as measured by diffusion-weighted magnetic resonance imaging, intracranial pressure, cerebral edema, and coagulopathy may elucidate how selective cerebral cooling can serve as an adjunctive treatment for cerebral ischemia.

Conclusions

The feasibility of selective retrograde cerebral cooling through the internal jugular vein has been established in a porcine model of complete cerebral circulatory arrest. Neurologic assessments of animals undergoing this therapy reflected substantial neuroprotection in up to 30 min of otherwise catastrophic interruption of cerebral blood flow. Cerebral cooling to <30°C was achieved within a reasonable therapeutic time frame and did not result in additional deleterious effects seen with systemic cooling. Our cadaveric study demonstrates that this technique is feasible in the adult human anatomy. These results support the need for further studies of selective retrograde cerebral cooling as an adjunct treatment in the management of ischemic events including AIS.

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Conflicts of interest

BCV, MERJ, ILB, JMO, RDS hold stock in Voyage Biomedical Inc.

References

1. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, 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. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-110.
3. de Los Ríos la Rosa F, Khoury J, Kissela BM, Flaherty ML, Alwell K, Moomaw CJ, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population: The effect of the European Cooperative Acute Stroke Study (ECASS) III trial. Stroke 2012;43:1591-5.
4. Miller DJ, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic stroke: A review of complications risk factors and newer technologies. Neurohospitalist 2011;1:138-47.
5. Chia NH, Leyden JM, Newbury J, Jannes J, Kleining TJ. Determining the number of ischemic strokes potentially eligible for endovascular thrombectomy: A population-based study. Stroke 2016;47:1377-80.
6. McMeekin P, White P, James MA, Price CJ, Flynn D, Ford GA. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. Eur Stroke J 2017;2:319-26.
7. Smith EE, Saver JL, Cox M, Liang L, Matsouaka R, Xian Y, et al. Increase in endovascular therapy in get with the guidelines-stroke after the publication of pivotal trials. Circulation 2017;136:2503-10.
8. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200-15.
9. Harrison MW, Young A. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke [Internet]. The J Emerg Med 2019;57:273-4.
10. McCullough JN, Zhang N, Reich DL, Juvonen TS, Klein JJ, Spielvogel D, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 1999;67:1895-9.
11. Allen BS, Ko Y, Buckberg GD, Tan Z. Studies of isolated global brain ischaemia: III. Influence of pulsatile flow during cerebral perfusion and its link to consistent full neurological recovery with controlled reperfusion following 30 min of global brain ischaemia. Eur J Cardiothorac Surg 2012;41:1155-63.
12. Castellá M, Buckberg GD, Tan Z. Neurologic preservation by Na+-H+ exchange inhibition prior to 90 minutes of hypothermic circulatory arrest. Ann Thorac Surg 2005;79:646-54.
13. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186-202.
14. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: A “two-hit” model. Crit Care 2017;21:90.
15. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008;371:1955-69.
16. Olsen TS, Weber UJ, Kammersgaard LP. Therapeutic hypothermia for acute stroke. Lancet Neurol 2003;2:410-6.
17. Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. Lancet 1966;2:1113-5.
18. Choi JH, Marshall RS, Neimark MA, Konstas AA, Lin E, Chiang YT, et al. Selective brain cooling with endovascular intracarotid infusion of cold saline: A pilot feasibility study. AJNR Am J Neuroradiol 2010;31:928-34.
19. Ding Y, Yao B, Zhou Y, Park H, McAllister JP, Diaz FG. Prereperfusion flushing of ischemic territory: A therapeutic study in which histological and behavioral assessments were used to measure ischemia—reperfusion injury in rats with stroke [Internet]. J Neurosurg 2002;96:310-9.
20. de Bakey ME, Crawford ES, Cooley DA, Morris GC Jr., Successful resection of fusiform aneurysm of aortic arch with replacement by homograft. Surg Gynecol Obstet 1957;105:657-64.
21. Bakey ME, De Bakey ME. Successful resection of aneurysm of distal aortic arch and replacement by graft [Internet]. J American Med Assoc 1954;155:1398.
22. Englum BR, He X, Gulack BC, Ganapathi AM, Mathew JP, et al.
Brennan JM, et al. Hypothermia and cerebral protection strategies in aortic arch surgery: A comparative effectiveness analysis from the STS adult cardiac surgery database. Eur J Cardiothorac Surg 2017;52:492-8.

23. Yan TD, Bannon PG, Bavaria J, Coselli JS, Elefteriades JA, Griep RB, et al. Consensus on hypothermia in aortic arch surgery. Ann Cardiothorac Surg 2013;2:163-8.

24. Cohn LH. Cardiac Surgery in the Adult. 3rd ed. New York: McGraw Hill Professional; 2007.

25. Kayatta MO, Chen EP. Optimal temperature management in aortic arch operations. Gen Thorac Cardiovasc Surg 2016;64:639-50.

26. Nojima T, Magara T, Nakajima Y, Watarida S, Onoe M, Sugita T, et al. Optimal perfusion pressure for experimental retrograde cerebral perfusion. J Card Surg 1994;9:548-59.

27. Donnino MW, Andersen LW, Berg KM, Reynolds JC, Nolan JP, Morley PT, et al. Temperature management after cardiac arrest: An advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the American Heart Association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, peroperative and resuscitation. Resuscitation 2016;98:97-104.

28. Nielsen N, Weterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197-206.

29. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med 2019;381:2327-37.

30. Nordberg P, Taccone FS, Truhlar A, Forsberg S, Hollenberg J, Jonsson M, et al. Effect of trans-nasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: The PRINCESS randomized clinical Trial. JAMA 2019;321:1675-87.

31. Calabrò L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Soreide E, et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: A systematic review and meta-analysis. Crit Care 2019;23:285.

32. Perbet S, Mongardon N, Bruel C, Lemiale V, Calabrò L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Nordberg P, Taccone FS, Truhlar A, Forsberg S, Hollenberg J, Jonsson M, et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: A systematic review and meta-analysis. Crit Care 2019;23:285.

33. Nielsen N, Weterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Temperature management after cardiac arrest: An advisory statement by the advanced life support task force of the international liaison committee on resuscitation and the American Heart Association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, peroperative and resuscitation. Resuscitation 2016;98:97-104.

34. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Stepken J, Kudsk K, et al. The Danish Multicenter, Randomized, Phase III Clinical Trial of Therapeutic Hypothermia plus Best Medical Treatment vs Best Medical Treatment Alone for Acute Ischemic Stroke [Internet]. Int J Stroke 2014;9:642-5.

35. Ji YB, Wu YM, Ji Z, Song W, Xu SY, Wang Y, et al. Interrupted intracarotid artery cold saline infusion as an alternative method for neuroprotection after ischemic stroke. Neurosurg Focus 2012;33:E10.

36. Ding Y, Li J, Luan X, Lai Q, McAllister JP 2nd, Phillips JW, et al. Local saline infusion into ischemic territory induces regional brain cooling and neuroprotection in rats with transient middle cerebral artery occlusion. Neurosurgery 2004;54:596-604.

37. de Georgia MA, Krieger DW, Abou-Chedid A, Devlin TG, Jauss M, Davis SM, et al. COOL: A feasibility trial of endovascular cooling [Internet]. J Neurointerv Surg 2013;5:299-302.

38. Lownie SP, Menkis AH, Liwcinko JR, Gray-Edwards HL, et al. Focal cooling of brain parenchyma in a transient large vessel occlusion model: Proof-of-concept. J Neurointerv Surg 2019;1:6.

39. van der Worp HB, Macleod MR, Bath PM, Demotes M, Perrotin F, Durand-Zaïeski I, Gebbard B, et al. EuroHYP-1: European Multicenter, Randomized, Phase III Clinical Trial of Therapeutic Hypothermia plus Best Medical Treatment vs Best Medical Treatment Alone for Acute Ischemic Stroke [Internet]. Int J Stroke 2014;9:642-5.

30. Cohn LH. Cardiac Surgery in the Adult. 3rd ed. New York: McGraw Hill Professional; 2007.

31. Calabrò L, Bougouin W, Cariou A, De Fazio C, Skrifvars M, Soreide E, et al. Effect of different methods of cooling for targeted temperature management on outcome after cardiac arrest: A systematic review and meta-analysis. Crit Care 2019;23:285.