Review Article

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Quick Response Code:
Website:
http://www.braincirculation.org
DOI:
10.4103/bc.bc_23_19

From systemic to selective brain cooling – Methods in review

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Abstract:

Therapeutic hypothermia (TH) remains one of the few proven neuroprotective modalities available in clinical practice today. Although targeting lower temperatures during TH seems to benefit ischemic brain cells, systemic side effects associated with global hypothermia limit its clinical applicability. Therefore, the ability to selectively reduce the temperature of the brain while minimally impacting core temperature allows for maximizing neurological benefit over systemic complications. In that scenario, selective brain cooling (SBC) has emerged as a promising modality of TH. In this report, we reviewed the general concepts of TH, from systemic to selective brain hypothermia, and explored the different cooling strategies and respective evidence, including preclinical and clinical data. SBC has been investigated in different animal models with promising results, wherein organ-specific, rapid, and deep target brain temperature managements stand out as major advantages over systemic TH. Nevertheless, procedure-related complications and adverse events still remain a concern, limiting clinical translation. Different invasive and noninvasive methods for SBC have been clinically investigated with variable results, and although adverse effects were still reported in some studies, therapies rendered overall safe profiles. Further study is needed to define the optimal technique, timing of initiation, rate and length of cooling as well as target temperature and rewarming protocols for different indications.

Keywords:

Cooling methods, neuroprotection, selective brain cooling, selective brain hypothermia, therapeutic hypothermia

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Submission: 06-08-2019
Revised: 28-10-2019
Accepted: 05-11-2019

Introduction

Cardiac arrest (CA) is a significant cause of morbidity and mortality in the developed world. Approximately 350,000 out-of-hospital CAs occur annually in the US, and among the few who survive to discharge, <10% have preserved neurological function;[1] among those who do not make it to discharge, neurological complications are the leading cause of death.[2] Non-CA-related causes of severe brain injury are also associated with high morbidity and poor prognosis, and fever has been proven to be an independent risk factor for worse prognosis in neurocritically injured patients.[3-6]

Therapeutic hypothermia (TH) has been proven to favorably impact post-CA neurological outcomes and seems to benefit neonates with hypoxic-ischemic encephalopathy.[7-9] Although some types of neurological injuries yet lack evidence to support systematic TH, such as traumatic brain injury, controlled normothermia has been globally recommended after neurological injury in patients with refractory fever.[10,11]

Multiple factors contribute to neuroprotective effects derived from TH; early initiation and duration of therapy, cooling rate of the brain and its distribution, type of neurological injury, extension of ischemic insult, and occurrence of systemic adverse events derived from TH itself seem to directly impact neurological outcomes.[12-15] Distinct cooling methods have been clinically

How to cite this article: Assis FR, Narasimhan B, Ziai W, Tandri H. From systemic to selective brain cooling – Methods in review. Brain Circ 2019;5:179-86.

employed for temperature modulation, each of them with its own peculiarities.[16,17]

The ability to optimize selective (local) cooling while rendering the patient normothermic seems compelling as it reduces or eliminates the side effects associated with systemic hypothermia. Several invasive and noninvasive cooling strategies have been described as effective to generate a temperature gradient between brain and body (core) with encouraging results.[18] Nevertheless, most of them lack further clinical validation.

Herein, we review the main concepts of brain selective hypothermia, focusing on the different methods available and current data to support its clinical application.

Therapeutic Hypothermia – General Considerations

Consistent evidence has established the role of TH after CA.[19,20] Mild core temperature reduction (32°–36°) seems to confer a temperature range with neuroprotective benefit and which overcomes the potential side effects associated with whole-body cooling. Different TH strategies are currently available to induce and control core temperature. All methods collectively promote net heat loss by overcoming body thermoregulatory mechanisms. Regardless of the adopted strategy, systemic TH entails a broad spectrum of side effects and potential complications such as higher risk of infection, arrhythmia, coagulopathy, and hemodynamic compromise and by virtue of that should be applied with caution.[21]

Downregulation of cellular metabolism is the cornerstone of TH.[22,23] Ischemic injury triggers multiple deleterious chemical cascades that perpetuate the ischemic insult even after circulation is reestablished. The impact of TH on improving CA survival rates is systemic, as reflected by reduction of myocardial infarction scar and lower incidence of liver failure,[24,25] although neuroprotection is the main goal of this therapy. Reperfusion injuries, inflammation, disruption of the blood–brain barrier, and apoptosis are downmodulated by TH, wherein a 1°C drop results in a 5%–7% reduction in brain metabolism.[26-28] In addition, TH is associated with reduction of cerebral edema and intracranial pressure which further contribute to optimize cerebral perfusion pressure and thus minimize cerebral ischemic injury.[29,30] Although targeting lower temperatures during TH seems to benefit ischemic brain cells, systemic side effects associated with global hypothermia limit its clinical applicability.[31] In that scenario, selective brain cooling (SBC) has gained interest as a compelling and feasible approach to maximize neurological benefit over systemic complications.

Cooling methods – Overview

Several clinical temperature modulation methods are currently available for TH. Cold fluid infusion is an extensively studied strategy for hypothermia induction; however, although an efficient method to rapidly induce hypothermia, it lacks accurate temperature control and thus has not yet been validated for temperature maintenance.[32,33] In addition, it may be associated with lower survival rates among patients with pulseless electrical activity or asystole.[34] Although pulmonary edema and higher rates of vasopressor utilization have been previously associated with cold infusion, overall data seem to support its safety in different settings.[35] Surface cooling methods are reasonably effective, but require constant care (labor intensive), sedation, and are more prone to induce vasoconstriction and shivering, which might limit temperature reduction (via heat generation).[17,36] Catheters for intravascular cooling promote accurate temperature control; however, as an invasive strategy, its utilization is restricted to high complexity care units, inherits the risks of catheter-related complications, and is associated with higher health-care costs.[37,38] Extracorporeal blood cooling seems to be effective but not easily available as it demands specific expertise and specialized centers.[39]

Intra- or transnasal cooling has emerged as a promising TH strategy. Transnasal perfluorocarbon (PFC) spray in combination with high-flow oxygen has shown encouraging results in clinical studies including brain-injured patients requiring temperature control and as a suitable out-of-hospital method for early TH.[40,41] Similarly, transnasal high flow of dry air seems to safely induce and maintain either normothermia or hypothermia in preclinical models and preliminary clinical data.[42,43] Intranasal balloons circulated with cold saline safely provided brain temperature reduction and are well tolerated in awake patients.[44,45] Esophageal cooling devices circulating water at adjustable temperature have been shown to induce and accurately control core temperature in CA survivors without major adverse events. Nevertheless, when used alone, a long delay to start cooling (5 h) and to reach the target temperature (9 h) may favor its use in combination with other strategies.[46]

Selective Brain Cooling

SBC consists of globally or partially lowering the brain temperature to below that of arterial blood (core temperature).[47] Creating a net temperature gradient between body (core) and brain in an effort to avoid systemic hypothermia while applying local cooling allows for lowering overall risks during neuroprotective efforts.

Although brain heat loss and temperature control mechanisms are not quite clear in humans, modulation of brain temperature seems to rely upon a complex interaction between the superficial (face and upper airways) and deep vascular beds, wherein cooling both surface (heat loss through the skull and venous sinuses) and upper airways (mucosa) contributes to heat exchange.[48] Nevertheless, cerebral blood flow and the temperature of incoming arterial blood play a major role in brain temperature regulation.[49]

SBC usually promotes faster, deeper, and more organ-specific temperature reduction as compared to systemic TH.[50] Cerebral hypothermia has been shown to improve neurological outcomes in different settings, wherein even small reductions in brain temperature were associated with reduction of neurological injury after global or focal ischemia in animal models.[51] Distinct methods have been reported as feasible options for SBC although, despite promising preclinical data, few methods for selective TH are currently available for clinical use.[50] Local surface cooling through caps, helmets, and neckbands has proven to improve neurological outcomes; however, a temperature gradient across different regions in the brain (superficial vs. deep regions) may occur.[52] Heat exchange through intranasal cooling is a result of both direct heat loss to air and evaporation of water and can reach up to 10% of total body heat loss in normal conditions. Airflow rate, humidity, and temperature are determinant to net transnasal cooling effect.[53,54] Invasive methods have been also reported, and although effective, associated risk of infection, intracranial bleeding, and other limitations turn them into a less attractive option when a noninvasive alternative is available. Table 1 shows several clinical studies encompassing different methods for SBC.

As temperature assessment is key for adequate TH, SBC entails constraints since no risk-free invasive monitoring approach is feasible. Tympanic temperature readout and magnetic resonance techniques are currently available as validated noninvasive methods to assess brain temperature. Tympanic temperature can be used as a surrogate for brain temperature when properly measured, although arterial blood as supplied by external carotid artery may better represent face (superficial) rather than brain (deep) temperature.[65] This is especially true when rapidly inducing or reversing hypothermia.[66] Magnetic resonance thermometry constitutes a noninvasive alternative to measure brain temperature, providing not only accurate reading of absolute temperature but also temperature distribution across different regions of the brain.[67] Nevertheless, its utilization for continuous monitoring in clinical settings is impractical.

Intranasal cooling

The nasal apparatus is a well-vascularized structure that efficiently interacts with an enormous amount of air, which is received, circulated, and primed before reaching the lungs warm, clean, and humidified. The total surface of both nasal cavities reaches about 150 cm^2 and the total volume is about 15 ml. About 10,000 L/day of air passes through the nose at different flow rates and temperatures, and approximately 40 ml of nasal mucus is produced per day.[68,69] The venous system of the nose is composed of a complex interaction between the orbit, the sinuses, and the cavernous sinus, which converge along with other structures to form the turbinates, the major protagonists in upper airway heat exchange. Changes in vascular compliance as a response to autonomic tone directly impact on nasal mucosa ability to exchange heat and to control temperature.[70] While vasoconstriction associated with sympathetic predominance reduces local blood flow and thus impairs heat loss, parasympathetic stimulation causes vasodilation and increases mucus production.

Harnessing the aforementioned anatomical and physiological properties of the nose to promote either systemic or selective temperature control has led to the emergence of distinct cooling methods. Intranasal balloons circulated with cold saline reduce the brain temperature under conditions of both normal circulation and after CA.[44] Conduction cooling (local cooling) accounts for surrounding brain structures to cool faster than the rest during the initial phase, and progressive hematogenous spread of cooled blood leads to homogeneous distribution of the cooling effect throughout the brain and the body. At normal circulation settings, once core temperature is reduced, cooling rate decreases and further brain temperature drop becomes more dependent on core temperature reduction, occurring then at similar rates. At low circulation states, however, the global distribution of the cooling effect is restricted, and the brain is thus preferentially cooled over the body since conductive cooling runs independent of the underlying circulation.[71] Transnasal evaporative cooling (TEC) relies on energy dissipation (heat exchange) generated while blowing high flow of dry air or oxygen with PEC (liquid coolant) into the nose.[42,72] The process of nasal mucosa water evaporation generates heat loss and subsequent temperature reduction, to which both conductive and connective cooling further contribute. The cooling effect appears to be highly dependent on the airflow rate and air dryness, as lower flow rates and humidification of the inflowing air mitigate the cooling effect.[73]

The PRINCE trial, a randomized multicenter study, investigated the effects of TEC using a mixture of PFC and high-flow oxygen in patients with witnessed CA and

Table 1: Clinical studies on different methods of selective brain cooling

Author	Years	Patients (*n*)	Population	Method	Results	Adverse events
				Surface cooling		
Corbett and Laptook[55]	1998	10	Health volunteers	Double-layer head–neck cooling pads	Failed to reduce brain temperature, with no gradient between superficial and deep brain	None
Wang *et al.*[56]	2004	14 (6 controls)	Neurocritical (severe stroke or head injury)	Cooling helmet	Rapid SBC (average reduction of −1.6°C) with delayed systemic temperature reduction	Asymptomatic bradycardia (1)
Gluckman *et al.*[57]	2005	234 (118 controls)	Neonates (HIE)	Cooling caps	Reduction in the rate of disabling neurodevelopmental sequelae in patients with less severe EEG abnormalities	No significant difference between cases and controls
Poli *et al.*[58]	2013	11	Severe stroke patients	Head–neck cooling device	Lower reduction of brain temperature when compared with other methods. Transient elevation of ICP and blood pressure	Severe HTN (3), ICP increase by >10 mmHg (3), and drop in CPP to <50 mmHg (1)
				Intranasal cooling		
Castrén *et al.*[41]	2010	200 (104 controls)	Out-of-hospital CA survivors	Intranasal cooling (PFC)	Although no significant difference was observed in overall survival rate (cooling vs. control), patients with early CPR presented higher rates of survival to discharge	Periorbital emphysema (1), epistaxis (3), perioral bleed (1), and nasal mucosa discoloration (13)
Abou-Chebl *et al.*[40]	2011	15	Intracerebral hemorrhage, trauma, and stroke patients (fever)	Intranasal (PFC)	Fast reduction of brain and core temperature, with the former occurring first. No major complication	HTN (1)
Poli *et al.*[59]	2014	20 (10 cold infusion/10 intranasal)	Intubated stroke patients	Cold infusion and intranasal cooling	Cold infusion induced faster brain temperature reduction than intranasal cooling. Deleterious effects on blood pressure and ICP were noted in both groups	Cold infusion: HTN (7), shivering (1) Intranasal: HTN (6), shivering (1)
Chava *et al.*[60]	2019	32 (16 controls)	Intubated patients undergoing electrophysiological procedures	Intranasal cooling (dry air)	Reduction of core temperature in healthy individuals	None
Ziai *et al.*[43]	2019	7	Febrile neurocritical patients	Intranasal cooling (dry air)	Reduction of core temperature. Five patients rendered normothermic after 2 h of therapy	None
Seyedsaadat *et al.*[61]	2019	5	Adults undergoing aortic valve replacement with cardiopulmonary bypass support (few patients)	Esophageal and intranasal cooling (circulated cold infusion)	Fast reduction of brain temperature. A temperature gradient between brain and body was observed	Postprocedure (unrelated to cooling strategy)
				Intravascular cooling		
Choi *et al.*[62]	2010	18	Patients undergoing follow-up cerebral angiography after treatment of vascular malformations	Intra-arterial infusion of cold saline (internal carotid artery)	Rapid reduction of brain temperature. No systemic or adverse effects reported	None
Chen *et al.*[63]	2016	26	Acute ischemic stroke (<8 h) who underwent successful endovascular recanalization (large vessel occlusion)	Intra-arterial infusion of cold saline (culprit artery)	Reduced the temperature in the ischemic cerebral tissue (minimum 2°C reduction) with mild reduction in systemic temperature (maximum 0.3°C). No related complications reported	Vascular spasm (4), coagulopathy (2), pneumonia (10), DVT (1), melena (2), and neurological deterioration (4)
Peng *et al.*[64]	2016	11	Acute ischemic (middle cerebral artery occlusion; <6 h) undergoing endovascular recanalization	Intra-arterial infusion of cold saline (pre-reperfusion)	Therapy was associated with smaller infarct volumes and greater improvement of neurological deficits	None

CPP: Cerebral perfusion pressure, CPR: Cardiopulmonary resuscitation, DVT: Deep vein thrombosis, EEG: Electroencephalogram, HIE: Hypoxic-ischemic encephalopathy, HTN: Hypertension, ICP: Intracranial pressure, PFC: Perfluorocarbon, SBC: Selective brain cooling, CA: Cardiac arrest early cardiopulmonary resuscitation (CPR) response. This was the first randomized study to demonstrate that intra-arrest TEC is feasible, safe, and associated with improved neurological outcomes; in patients who received CPR within 10 min after CA, intranasal cooling was associated with a significant increase in survival to discharge rates and neurologically intact survival to discharge, when compared to standard of care (56.5% vs. 29.4%, $P = 0.04$; 43.5% vs. 17.6%, $P = 0.03$, respectively).[41] Covaciu *et al*. reported a uniform brain temperature reduction in conscious volunteers under intranasal cooling using balloon catheters circulated with cold saline with cold water for a 60-min period. Different cooling rates between brain and rectal temperatures indicated preferential brain cooling, and therapy was well tolerated.[45] Chava *et al*., in a study including 23 intubated subjects, showed that transnasal high flow (30 L/min) of dry air, after 1 h of therapy, significantly reduced core (esophageal) temperature as compared to controls (36.1 ± 0.3–35.5 ± 0.1; $P < 0.05$ [transnasal cooling] vs. 36.3 ± 0.3–36.2 ± 0.2; P = NS [controls]), with no adverse events.[60]

Surface cooling

Different surface cooling strategies for selective brain temperature reduction have been explored, including cooling caps, helmets, and head–neck devices. In a study with newborn pigs which underwent a global ischemic insult, a cooling cap was able to significantly reduce deep brain temperature while preserving mild systemic hypothermia during a 24-h period, with a median gradient between brain and rectal temperature of 3.4°C (interquartile range: 2.9–3.7°C).[74] A randomized multicenter trial including 234 neonates with hypoxic-ischemic encephalopathy also using a cooling cap to preferentially cool the brain under mild hypothermia reduced the rate of disabling neurodevelopmental sequelae in those patients with less severe electroencephalogram abnormalities.[57] In a study with 25 patients with severe traumatic brain injury (Glasgow Coma Scale <8), the utilization of a cooling helmet failed to demonstrate significant difference between brain–bladder temperature gradients during 24-h selective cooling (helmet) as compared to usual care, and no mortality benefit was noted.[75]

In a larger trial including 90 patients with severe traumatic brain injury, half of the patients underwent to SBC using a combination of a head cooling cap (4°C water) and neckband cooling in addition to standard of care (interventional group); the other half underwent standard of care alone (control group).[52] In the intervention group, selective cooling was successfully attained while preserving core temperature within the normothermic range, and average intracranial pressure was significantly lower when compared to the control group. Patients receiving selective cooling also showed higher good neurological outcome rates versus controls (68.9 vs. 46.7%, $P < 0.05$) at 6-month of follow-up, with no severe complications reported.

Invasive cooling

Harnessing heat exchange properties of brain vasculature using intra- or extravascular invasive methods has been investigated as an efficient alternative to promote SBC. Although cardiovascular complications associated with secondary systemic hypothermia induced by invasive brain cooling have been early reported,[76,77] improvement on modeling and the ability to safely sustain a brain-core temperature gradient within the system normothermic temperature range accounted for positive neurological outcomes while minimizing cardiovascular complications. Extracorporeal cooling of the blood using a closed-loop system, through which blood drawn from the femoral artery (outflow) was externally cooled and pumped backed into either carotid arteries or their branches (inflow), successfully demonstrated neuroprotective effects of brain cooling in normothermic animal models.[78,79] In one of these studies, unilateral perfusion of cooled blood through the right internal carotid was able to selectively cool the brain bilaterally.

Intracarotid infusion of cold saline (0°C) in early CA animal models showed good neurological outcomes,[80,81] and retrograde infusion of cold saline (4°C) through the external jugular vein allowed for fast reduction of brain temperature in rat models.[82] When comparing intracarotid cold saline infusion, cooling cap, and a combination of both, cooling cap alone was not capable of achieving cold temperatures in deep brain, in accordance with prior reports.[83] Extraluminal cooling of the common carotid artery using a cooled cuff surrounding the vessel has been successfully described, showing a reduction of cerebral infarct size after transient middle cerebral artery occlusion in rats.[84] Intra-arterial infusion of cold saline directly into the culprit artery in patients with ischemic strokes undergoing endovascular recanalization was able to selectively reduce brain temperature and was associated with smaller infarct size and better neurological outcomes.[63,64]

Overall, the utilization of vascular strategies to selectively modulate brain temperature seems to be effective in distinct animal clinical models, with a significant reduction of complications when systemic normothermia is preserved. However, the risk associated with the manipulation of such vessels discourages and limits translational efforts toward clinical applicability. Furthermore, cooling distribution also relies on vascular patency and by virtue of that might be impaired in situations where cerebral perfusion is compromised focally, as in ischemic strokes, or globally, as in traumatic brain injury.[18]

Compartmental cooling

Intracranial compartmental cooling to induce selective brain hypothermia consists of an invasive approach to directly modulate cerebral temperature using conductive or connective cooling strategies. Similar to intravascular methods, the infusion of cold saline solution into epidural, subdural, subarachnoid, and intraventricular spaces has demonstrated to reduce brain temperature in preclinical and clinical studies with interesting results. In porcine models, epidural drip of cold saline rapidly reduced cerebral parenchymal temperature, whereas brain distribution of the temperature was not assessed.[85] Local circulation of cold saline within a pad, placed directly over the dura, was able to cool the brain in a primate traumatic brain injury model; however, brain temperature was not uniformly distributed.[86] Such a temperature gradient between deep and superficial parenchyma (greater temperature closer to the cooling source) was also observed in a cat model with middle cerebral artery occlusion, wherein subdural infusion of cold saline also demonstrated SBC with reduction of cortical edema.[87] In a clinical trial including 25 patients with intractable epilepsy, deep anesthesia in combination with both systemic and local hypothermia through cold irrigation of the subarachnoid space significantly reduced brain temperature; however, deep brain temperature increased 2°C/10 mm from the surface (cortex); eleven patients presented a reduction in the frequency and intensity of the seizures.[88]

Different methods for intraventricular cooling using cold infusion have been reported. Controlled infusion of cold saline (7–10 ml/min) under ICP monitoring (1–5 cm^2O) in dogs demonstrated a significant reduction in brain temperature to as low as 13°C, with an uneven distribution of temperature drop between infra- and supratentorial compartments. Even though a reduction in core temperature occurred, a significant cortical-systemic temperature gradient was again evident.[89] Tokuoka *et al*. reported three psychiatric cases in which cold intraventricular infusion (8°C) was employed without complications. The lateral ventricle was used as an influent site in all cases, while the effluent site varied (cisterna magna in two cases and contralateral lateral ventricle in the remainder case).[90]

Overall, compartmental cooling strategies have demonstrated SBC since early preclinical trials. Epidural, subdural, and subarachnoid cooling strategies collectively seem to preferentially cool the cortex, although subdural cooling may affect a greater area. All methods are vulnerable to anatomical restriction (epidural adhesions, subarachnoid vasculature, intraventricular obstructions, etc.), which may increase risks of the procedure and impair heat exchange efficiency and distribution.

Summary

TH has been shown to benefit patients with focal or global acute cerebral injury. Selective brain hypothermia appears to enhance neuroprotective effects as it promotes faster and organ-selective cooling with minimal impact on core temperature and thereby mitigates systemic side effects. Preclinical and clinical data have demonstrated its safety and efficacy to improve neurological outcomes in different settings through varied methods. Although invasive methods seem to promote rapid and stable whole-brain temperature reduction, they afford a higher risk of procedure-related complications, and by virtue of that, less invasive methods constitute a safer and fair alternative for selective TH. Nevertheless, further clinical assessment is warranted to define the optimal method and indications, timing of initiation, rate and length of cooling as well as target temperature and rewarming protocols.

Financial support and sponsorship

Nil.

Conflicts of interest

Harikrishna Tandri is the founder of CoolTech Inc., which is developing a transnasal device for hypothermia.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, *et al.* Heart disease and stroke statistics-2018 update: A report from the American Heart Association. Circulation 2018;137:e67-492.
2. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: A randomized trial. JAMA 2009;302:2222-9.
3. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. Crit Care Med 2004;32:1489-95.
4. Kilpatrick MM, Lowry DW, Firlik AD, Yonas H, Marion DW. Hyperthermia in the neurosurgical intensive care unit. Neurosurgery 2000;47:850-5.
5. Wang CX, Stroink A, Casto JM, Kattner K. Hyperthermia exacerbates ischaemic brain injury. Int J Stroke 2009;4:274-84.
6. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: A comprehensive meta-analysis. Stroke 2008;39:3029-35.
7. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, *et al.* Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
8. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
9. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, *et al.* Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84.
10. Watson HI, Shepherd AA, Rhodes JKJ, Andrews PJD. Revisited: A systematic review of therapeutic hypothermia for adult patients

following traumatic brain injury. Crit Care Med 2018;46:972-9.
11. Madden LK, Hill M, May TL, Human T, Guanci MM, Jacobi J, *et al.* The implementation of targeted temperature management: An evidence-based guideline from the neurocritical care society. Neurocrit Care 2017;27:468-87.
12. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study. Crit Care Med 1993;21:1348-58.
13. MacLellan CL, Girgis J, Colbourne F. Delayed onset of prolonged hypothermia improves outcome after intracerebral hemorrhage in rats. J Cereb Blood Flow Metab 2004;24:432-40.
14. Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Müllner M. Hypothermia for neuroprotection after cardiac arrest: Systematic review and individual patient data meta-analysis. Crit Care Med 2005;33:414-8.
15. Gunn AJ. Cerebral hypothermia for prevention of brain injury following perinatal asphyxia. Curr Opin Pediatr 2000;12:111-5.
16. Seder DB, Van der Kloot TE. Methods of cooling: Practical aspects of therapeutic temperature management. Crit Care Med 2009;37:S211-22.
17. 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.
18. Straus D, Prasad V, Munoz L. Selective therapeutic hypothermia: A review of invasive and noninvasive techniques. Arq Neuropsiquiatr 2011;69:981-7.
19. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, *et al.* European resuscitation council and european society of intensive care medicine guidelines for post-resuscitation care 2015: Section 5 of the european resuscitation council guidelines for resuscitation 2015. Resuscitation 2015;95:202-22.
20. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, *et al.* Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S465-82.
21. Wijdicks EF. Induced hypothermia in neurocatastrophes: Feeling the chill. Rev Neurol Dis 2004;1:10-5.
22. Yenari M, Kitagawa K, Lyden P, Perez-Pinzon M. Metabolic downregulation: A key to successful neuroprotection? Stroke 2008;39:2910-7.
23. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab 2003;23:513-30.
24. Stravitz RT, Larsen FS. Therapeutic hypothermia for acute liver failure. Crit Care Med 2009;37:S258-64.
25. Hale SL, Kloner RA. Myocardial temperature reduction attenuates necrosis after prolonged ischemia in rabbits. Cardiovasc Res 1998;40:502-7.
26. Neumar RW. Molecular mechanisms of ischemic neuronal injury. Ann Emerg Med 2000;36:483-506.
27. Milde LN. Clinical use of mild hypothermia for brain protection: A dream revisited. J Neurosurg Anesthesiol 1992;4:211-5.
28. Kumura E, Yoshimine T, Iwatsuki KI, Yamanaka K, Tanaka S, Hayakawa T, *et al.* Generation of nitric oxide and superoxide during reperfusion after focal cerebral ischemia in rats. Am J Physiol 1996;270:C748-52.
29. Polderman KH, Tjong Tjin Joe R, Peerdeman SM, Vandertop WP, Girbes AR. Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury. Intensive Care Med 2002;28:1563-73.
30. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. Stroke 1998;29:2461-6.
31. Scirica BM. Therapeutic hypothermia after cardiac arrest. Circulation 2013;127:244-50.
32. Kliegel A, Janata A, Wandaller C, Uray T, Spiel A, Losert H, *et al.* Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation 2007;73:46-53.
33. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, *et al.* Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: A randomized controlled trial. Circulation 2010;122:737-42.
34. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: A preliminary report. Resuscitation 2003;56:9-13.
35. Arulkumaran N, Suleman R, Ball J. Use of ice-cold crystalloid for inducing mild therapeutic hypothermia following out-of-hospital cardiac arrest. Resuscitation 2012;83:151-8.
36. Sessler DI, Moayeri A, Støen R, Glosten B, Hynson J, McGuire J. Thermoregulatory vasoconstriction decreases cutaneous heat loss. Anesthesiology 1990;73:656-60.
37. Polderman KH, Callaghan J. Equipment review: Cooling catheters to induce therapeutic hypothermia? Crit Care 2006;10:234.
38. Patel N, Nair SU, Gowd P, Gupta A, Morris D, Geronilla GG, *et al.* Central line associated blood stream infection related to cooling catheter in cardiac arrest survivors undergoing therapeutic hypothermia by endovascular cooling. Conn Med 2013;77:35-41.
39. Testori C, Holzer M, Sterz F, Stratil P, Hartner Z, Moscato F, *et al.* Rapid induction of mild therapeutic hypothermia by extracorporeal veno-venous blood cooling in humans. Resuscitation 2013;84:1051-5.
40. Abou-Chebl A, Sung G, Barbut D, Torbey M. Local brain temperature reduction through intranasal cooling with the RhinoChill device: Preliminary safety data in brain-injured patients. Stroke 2011;42:2164-9.
41. Castrén M, Nordberg P, Svensson L, Taccone F, Vincent JL, Desruelles D, *et al.* Intra-arrest transnasal evaporative cooling: A randomized, prehospital, multicenter study (PRINCE: Pre-ROSC intraNasal cooling effectiveness). Circulation 2010;122:729-36.
42. Assis FR, Bigelow MEG, Chava R, Sidhu S, Kolandaivelu A, Halperin H, *et al.* Efficacy and safety of transnasal coolStat cooling device to induce and maintain hypothermia. Ther Hypothermia Temp Manag 2019;9:108-17.
43. Ziai WC, Shah D, Assis FR, Tandri H, Geocadin RG. Feasibility and safety of transnasal high flow air to reduce core body temperature in febrile neurocritical care patients: A pilot study. Neurocrit Care 2019;31:280-7.
44. Covaciu L, Allers M, Enblad P, Lunderquist A, Wieloch T, Rubertsson S. Intranasal selective brain cooling in pigs. Resuscitation 2008;76:83-8.
45. Covaciu L, Weis J, Bengtsson C, Allers M, Lunderquist A, Ahlström H, *et al.* Brain temperature in volunteers subjected to intranasal cooling. Intensive Care Med 2011;37:1277-84.
46. Goury A, Poirson F, Chaput U, Voicu S, Garçon P, Beeken T, *et al.* Targeted temperature management using the "Esophageal cooling device" after cardiac arrest (the COOL study): A feasibility and safety study. Resuscitation 2017;121:54-61.
47. Blatteis C, Boulant J, Cabanac M, Cannon B, Freedman R, Gordon CJ, *et al*. Glossary of terms for thermal physiology. Jpn J Physiol 2001;51:245-80.
48. Zhu M, Ackerman JJ, Sukstanskii AL, Yablonskiy DA. How the body controls brain temperature: The temperature shielding effect of cerebral blood flow. J Appl Physiol (1985) 2006;101:1481-8.
49. Sukstanskii AL, Yablonskiy DA. Theoretical limits on brain cooling by external head cooling devices. Eur J Appl Physiol 2007;101:41-9.
50. Choi JH, Pile-Spellman J. Selective brain hypothermia. Handb Clin Neurol 2018;157:839-52.
51. Ginsberg MD, Sternau LL, Globus MY, Dietrich WD, Busto R.

Therapeutic modulation of brain temperature: Relevance to ischemic brain injury. Cerebrovasc Brain Metab Rev 1992;4:189-225.
52. Qiu W, Shen H, Zhang Y, Wang W, Liu W, Jiang Q, *et al.* Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. J Clin Neurosci 2006;13:995-1000.
53. Hanson Rde G. Respiratory heat loss at increased core temperature. J Appl Physiol 1974;37:103-7.
54. McFadden ER Jr. Respiratory heat and water exchange: Physiological and clinical implications. J Appl Physiol Respir Environ Exerc Physiol 1983;54:331-6.
55. Corbett RJ, Laptook AR. Failure of localized head cooling to reduce brain temperature in adult humans. Neuroreport 1998;9:2721-5.
56. Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, *et al.* Rapid and selective cerebral hypothermia achieved using a cooling helmet. J Neurosurg 2004;100:272-7.
57. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, *et al.* Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. Lancet 2005;365:663-70.
58. Poli S, Purrucker J, Priglinger M, Diedler J, Sykora M, Popp E, *et al.* Induction of cooling with a passive head and neck cooling device: Effects on brain temperature after stroke. Stroke 2013;44:708-13.
59. Poli S, Purrucker J, Priglinger M, Ebner M, Sykora M, Diedler J, *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.
60. Chava R, Zviman M, Assis FR, Raghavan MS, Halperin H, Maqbool F, *et al.* Effect of high flow transnasal dry air on core body temperature in intubated human subjects. Resuscitation 2019;134:49-54.
61. Seyedsaadat SM, Marasco SF, Daly DJ, McEgan R, Anderson J, Rodgers S, *et al.* Selective brain hypothermia: Feasibility and safety study of a novel method in five patients. Perfusion 2019. https://doi.org/10.1177/0267659119853950.
62. 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.
63. Chen J, Liu L, Zhang H, Geng X, Jiao L, Li G, *et al.* Endovascular hypothermia in acute ischemic stroke: Pilot study of selective intra-arterial cold saline infusion. Stroke 2016;47:1933-5.
64. Peng X, Wan Y, Liu W, Dan B, Lin L, Tang Z. Protective roles of intra-arterial mild hypothermia and arterial thrombolysis in acute cerebral infarction. Springerplus 2016;5:1988.
65. McCaffrey TV, McCook RD, Wurster RD. Effect of head skin temperature on tympanic and oral temperature in man. J Appl Physiol 1975;39:114-8.
66. Stone JG, Young WL, Smith CR, Solomon RA, Wald A, Ostapkovich N, *et al.* Do standard monitoring sites reflect true brain temperature when profound hypothermia is rapidly induced and reversed? Anesthesiology 1995;82:344-51.
67. Harris BA, Andrews PJ, Marshall I, Robinson TM, Murray GD. Forced convective head cooling device reduces human cross-sectional brain temperature measured by magnetic resonance: A non-randomized healthy volunteer pilot study. Br J Anaesth 2008;100:365-72.
68. Jones N. The nose and paranasal sinuses physiology and anatomy. Adv Drug Deliv Rev 2001;51:5-19.
69. Quraishi MS, Jones NS, Mason J. The rheology of nasal mucus: A review. Clin Otolaryngol Allied Sci 1998;23:403-13.
70. Lund VJ. Nasal physiology: Neurochemical receptors, nasal cycle, and ciliary action. Allergy Asthma Proc 1996;17:179-84.
71. Boller M, Lampe JW, Katz JM, Barbut D, Becker LB. Feasibility of intra-arrest hypothermia induction: A novel nasopharyngeal approach achieves preferential brain cooling. Resuscitation 2010;81:1025-30.
72. Boller MC, Lampe J, Becker LB. Feasibility of selective brain cooling during cardiac arrest: A novel nasopharyngeal approach. Circulation 2007;116:II_944.
73. Chava R, Zviman M, Raghavan MS, Halperin H, Maqbool F, Geocadin R, *et al.* Rapid induction of therapeutic hypothermia using transnasal high flow dry air. Ther Hypothermia Temp Manag 2017;7:50-6.
74. Tooley J, Satas S, Eagle R, Silver IA, Thoresen M. Significant selective head cooling can be maintained long-term after global hypoxia ischemia in newborn piglets. Pediatrics 2002;109:643-9.
75. Harris OA, Muh CR, Surles MC, Pan Y, Rozycki G, Macleod J, *et al.* Discrete cerebral hypothermia in the management of traumatic brain injury: A randomized controlled trial. J Neurosurg 2009;110:1256-64.
76. Parkins WM, Jensen JM, Vars HM. Brain cooling in the prevention of brain damage during periods of circulatory occlusion in dogs. Ann Surg 1954;140:284-9.
77. Kimoto S, Sugie S, Asano K. Open heart surgery under direct vision with the aid of brain-cooling by irrigation; experimental studies and report of clinical cases, including three successfully treated cases of atrial septal defect. Surgery 1956;39:592-603.
78. Cheng H, Ji X, Ding Y, Luo Y, Wang G, Sun X, *et al.* Focal perfusion of circulating cooled blood reduces the infarction volume and improves neurological outcome in middle cerebral artery occlusion. Neurol Res 2009;31:340-5.
79. Schwartz AE, Stone JG, Finck AD, Sandhu AA, Mongero LB, Adams DC, *et al.* Isolated cerebral hypothermia by single carotid artery perfusion of extracorporeally cooled blood in baboons. Neurosurgery 1996;39:577-81.
80. Wolfson SK Jr., Inouye WY, Kavianian A, Icoz MV, Parkins WM. Preferential cerebral hypothermia for circulatory arrest. Surgery 1965;57:846-55.
81. Bacalzo LV Jr., Wolfson SK Jr. Resuscitation after unexpected circulatory arrest: Tolerance to cerebral ischemia provided by cold carotid perfusion. Biomed Sci Instrum 1969;5:75-8.
82. Wen YS, Huang MS, Lin MT, Lee CH. Rapid brain cooling by hypothermic retrograde jugular vein flush. J Trauma 2005;58:577-81.
83. Neimark MA, Konstas AA, Choi JH, Laine AF, Pile-Spellman J. Brain cooling maintenance with cooling cap following induction with intracarotid cold saline infusion: A quantitative model. J Theor Biol 2008;253:333-44.
84. Wei G, Hartings JA, Yang X, Tortella FC, Lu XC. Extraluminal cooling of bilateral common carotid arteries as a method to achieve selective brain cooling for neuroprotection. J Neurotrauma 2008;25:549-59.
85. Cheng H, Shi J, Zhang L, Zhang Q, Yin H, Wang L. Epidural cooling for selective brain hypothermia in porcine model. Acta Neurochir (Wien) 2006;148:559-64.
86. King C, Robinson T, Dixon CE, Rao GR, Larnard D, Nemoto CE. Brain temperature profiles during epidural cooling with the chillerPad in a monkey model of traumatic brain injury. J Neurotrauma 2010;27:1895-903.
87. Noguchi Y, Nishio S, Kawauchi M, Asari S, Ohmoto T. A new method of inducing selective brain hypothermia with saline perfusion into the subdural space: Effects on transient cerebral ischemia in cats. Acta Med Okayama 2002;56:279-86.
88. Sourek K, Trávnícek V. General and local hypothermia of the brain in the treatment of intractable epilepsy. J Neurosurg 1970;33:253-9.
89. Costal M, Owens G, Woldring S. Experimental production of cerebral hypothermia by ventricular perfusion techniques. J Neurosurg 1963;20:112-7.
90. Tokuoka S, Aoki H, Higashi K, Tatebayashi K, Nakamura T, Yokoyam I. Cerebral hypothermia by ventricular perfusion. Bull Yamaguchi Med Sch 1967;14:19-50.