Selective therapeutic hypothermia
A review of invasive and noninvasive techniques

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ABSTRACT

Objective: Therapeutic hypothermia is a promising treatment to prevent secondary neurologic injury. Clinical utility is limited by systemic complications of global hypothermia. Selective brain cooling remains a largely uninvestigated application. We review techniques of inducing selective brain cooling. **Method:** Literature review. **Results:** Strategies of inducing selective brain cooling were divided between non-invasive and invasive techniques. Non-invasive techniques were surface cooling and cooling via the upper airway. Invasive cooling methods include transvascular and compartmental (epidural, subdural, subarachnoid and intraventricular) cooling methods to remove heat from the brain. **Conclusion:** Selective brain cooling may offer the best strategy for achieving hypothermic neuroprotection. Non-invasive strategies have proven disappointing in human trials. There is a paucity of human experiments using invasive methods of selective brain cooling. Further application of invasive cooling strategies is needed.
Key words: therapeutic hypothermia, selective brain cooling, neuroprotection, isolated cerebral hypothermia.

Hipotermia terapêutica seletiva: uma revisão de técnicas invasivas e não invasivas

RESUMO

Objetivo: A hipotermia terapêutica é uma estratégia promissora para prevenção do dano neurológico secundário. Sua utilidade clínica é limitada por complicações sistêmicas da hipotermia global. Resfriamento cerebral seletivo (RCS), entretanto, permanece uma técnica pouco estudada. Revisamos aqui as diferentes técnicas de indução de RCS. **Método:** Revisão de literatura. **Resultados:** As estratégias de indução de RCS foram divididas em invasivas e não-invasivas. Métodos de remoção de calor do cérebro não-invasivos incluem o resfriamento de superfície e o de vias aéreas superiores; as técnicas invasivas incluem resfriamento transvascular e compartimental (epidural, subdural, subaracnóideo e intraventricular). **Conclusão:** RCS pode oferecer a melhor estratégia para alcançar neuroproteção hipotérmica. Estratégias não-invasivas têm se mostrado ineficazes em estudos clínicos. Técnicas invasivas foram raramente estudadas em humanos e necessitam ser mais investigadas para tornarem-se úteis.
Palavras-Chave: hipotermia terapêutica, resfriamento cerebral seletivo, neuroproteção, hipotermia cerebral isolada.

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Therapeutic hypothermia has been a subject of modern medical research since the 1940s. Significant laboratory evidence from animal and basic science studies supports the efficacy of hypothermia in preserving neurological function[1]. Neuroprotection via therapeutic hypothermia has been successfully implemented in the setting of cardiac arrest[2] and hypoxic-ischemic encephalopathy in newborns[3]. A series of negative or equivocal clinical trials in traumatic brain injury[4-6], stroke[7], cardiopulmonary bypass and intracranial aneurysm surgery[8], however, has undermined the clinical role for therapeutic hypothermia, despite the significant laboratory evidence

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supporting the efficacy of the technique in preserving neurological function[9]. Difficulties inducing hypothermia and systemic side effects of the therapy have proven to be significant obstacles to the application of therapeutic hypothermia to a broader spectrum of clinical disorders. Increased risk of infection, coagulopathy, cardiopulmonary compromise and risks of re-warming erode the clinical utility of systemic therapeutic hypothermia, offsetting any beneficial effects on neurological function and limiting the achievable depth of induced hypothermia[1,9]. Moreover, induction of systemic hypothermia exhibits a significant and unpredictable lag time from institution of therapy to achievement of target temperature[10].

Selective hypothermia, initially investigated in the 1960s prior to the advent of effective cardiopulmonary bypass, has re-emerged as a potential solution to the logistical obstacles and systemic complications of whole body hypothermia[11]. Descriptions of different methods to selectively cool the central nervous system (CNS) are numerous; however few have been thoroughly tested in clinical practice[11]. Given the paucity of therapeutic options for many neurological injuries, translation of the beneficial effects of therapeutic hypothermia noted in the laboratory to effective clinical applications at the bedside remains an area of interest. Selective therapeutic hypothermia offers a promising modality to realize the potential benefits of therapeutic hypothermia in the clinical arena.

In this article, we review the published strategies of selectively cooling the CNS. Additionally, we will argue that one direction of future research holds particular promise. We will consider separately noninvasive and invasive techniques of cooling. While the former enjoys obvious advantages, such as ease of implementation, most studies have shown very minimal ability to cool the parenchyma of the brain. In contrast, invasive methods of cooling remain a field in its infancy, with few human participant trials. This latter approach holds greater promise for the future of selective hypothermia.

Non invasive techniques of cooling

The upper airway – The beneficial role of systemic, therapeutic hypothermia after resuscitation from cardiac arrest has been well established[12,13]. However, cooling techniques remain suboptimal. In seminal trials establishing the role of mild hypothermia after cardiac arrest, systemic cooling was begun after return of spontaneous circulation, and associated with improved neurological outcomes. In contrast, animal have shown that early, and even intra-arrest cooling is associated with better outcomes, and diminished reperfusion injury[14-16].

In recent years, the technique of transnasal-evaporative cooling (TEC) has emerged as a potential solution

to the problem of delayed cooling. In TEC, a mixture of liquid coolant and oxygen is sprayed into the nasopharynx, and the liquid undergoes rapid evaporation under the administration of high flow oxygen[17]. The device is portable and results in rapid cooling of the nasal passages and brain. In animal studies, the device, when administered at the time of arrest, has been shown to result in a higher probability of restoration of spontaneous circulation, and improved neurological outcomes compared with cooling performed after resuscitation, applied systemically[18].

The randomized, multicenter trial pre-restoration of spontaneous circulation IntraNasal Cooling Effectiveness trial (PRINCE) sought to test whether TEC would improve neurological outcomes among victims of witnessed arrest compared to usual care. Regardless of arrest rhythm, patients with witnessed arrest, and prompt emercency medical services (EMS) response (<20 min) were randomized to intranasal cooling, or usual care involving cooling after hospital arrival. Standard European resuscitation guidelines governed EMS actions. Tympanic membrane temperature was monitored as a surrogate for deep brain temperature. The target temperature, which the authors achieved, was 34°C. TEC reached this temperature 129 minutes before usual care.

Although the study was not powered to detect differences in survival, the authors note a trend toward improved survival among the subset of patients admitted to the hospital (43.8% vs. 31.0%). In a further subset of patients for whom cardiopulmonary resuscitation (CPR) was initiated within 10 minutes of arrest, intranasal cooling was associated with a significant benefit in survival to hospital discharge (56.5% vs. 29.4%).

However, examining the overall numbers from PRINCE is disappointing. 93 patients were treated with the Rhinochill device, and 101 served as controls. Fourteen and 13 patients survived to hospital discharge, and nine and 11 were neurologically intact at that point, respectively. Thus, the raw numbers show no benefit. At least one reason for the null results may be that tympanic membrane temperature is likely not a valid surrogate for deep brain temperature[19]. Other groups have called into question whether externally measured temperatures have any correlation with deep brain ones[20].

Beyond evaporative methods, conductive cooling of the nasopharynx has also been employed in the quest for selective hypothermia. In rat models, flushing the nasopharynx with cold saline[21], or cold water passed through tygon tubing have both been attempted[22]. Others have extended these findings to large animal (pig) models[23]. Covaciu and colleagues anesthetized twelve pigs and performed selective cooling via a specially designed thin walled balloon catheter, placed in the nasopharynx

and flushed with cool water in a circuit with a Stöckert twin pump and a heat exchanger machine Stöckert heat-cooling unit (HCU). At baseline the parenchymal brain temperature was 38.1±0.6. After one hour of continuous cooling brain temperature was 35.3±0.6°C; after six hours brain temperature was 34.7±0.9°C.

Three studies of high flow gas through the upper airways all yielded null results. Einer-Jensen and Khorooshi[24] examine the effect of high flow oxygen though the nasopharnyx on brain temperature for 11 intubated adult rats. They noted a slight dose response of 0.25 degree Celsius drop in temperature at 250 mL/min flow, to a 0.75 degree Celsius drop at 1000 mL/min. Mellegard[25] applied high flow (5-10 L/min) humidified oxygen via foley catheter in one nostril to three intubated adult patients after trauma and hemorrhage. Cooling was applied for more than two hrs. Mellegard observed at best a 0.2 degree Celsius reduction in brain temperature, measured in the lateral ventricle. Finally, Andrews and Harris[26] performed a trial of air delivered at rates equivalent to minute ventilation via bilateral nasal cannulae to 15 patients who had suffered trauma or hemorrhage. No change in parenchymal or subdural temperature was observed.

Surface cooling of the head – Studies of convective air-cooling of the brain have yielded unimpressive results. Wass and colleagues[27] utilized a forced air-cooling helmet for 16 anesthetized dogs. They found at best a 2 degree Celsius drop in intraparenchymal temperature at a depth of 2cm, with an average drop of 0.5°C at that depth. Shiraki and colleagues[28] provide a case report of a single adolescent undergoing face fanning after surgery for a pineal tumor. Shiraki et al. report no convincing change in intracranial temperature from monitoring devices.

Tooley and colleagues[29] investigate the role of the cooling cap in providing selective hypothermia. Eight anesthetized newborn pigs underwent a hypoxia ischemia injury known to result in brain damage. They then were cooled with an externally placed cooling cap. Temperature of the scalp, dura, deep brain (measured in basal ganglia), and rectal temperature were monitored. The authors wanted to test the feasibility of selective brain cooling, while preserving core body temperature. Thus, overhead heat lamps were used to maintain a rectal temp of 35°C. The authors demonstrated that the deep brain temperature could be brought down to 31.4°C by this method. They also made the observation that scalp skin temperature did not correlate with deep brain temperature. This fact raises questions for other methods of intranasal cooling, which monitor only externally measured temperatures. Such surface temperatures are likely unreliable.

A similar technique of selective hypothermia via cooling cap was employed in a randomized trial of neonates with hypoxic-ischemic encephalopathy (HIE)[30]. Two hundred thirty-four babies with HIE were randomized to a cooling cap, and overhead heating for 72 hours within six days of birth or conventional care. The results were that 66% of those allocated to conventional care and 55% of those assigned head cooling died or had severe disability at 18 months (odds ratio 0.61; 95% CI 0.34-1.09, p=0.1). Prespecified subgroup analysis, based on severity of amplitude integrated electroencephalography (aEEG) findings demonstrated a subset of children who benefited from therapy. Those with less severe aEEG changes (n=172, 0.42; 0.22-0·80, p=0.009) had improvement of the primary outcome. However, though the subgroups were prespecified, such an analysis does not avoid the limitations of subgroup analyses, most notably inflated false positive rates from multiple testing[31]. While these results are encouraging for neonatal care, they are not easily generalizable to an adult population given the unique anatomy and intracranial dynamics of newborns.

Harris and colleagues performed a randomized controlled trial of a cooling helmet among adults presenting with a traumatic brain injury (TBI). Adults admitted with TBI who had Glasgow coma scores (GCS) of <8 were randomized to a cooling helmet, and selective hypothermia for 24 hours or usual care. The trial was hindered by poor enrollment, and ultimately twelve patients underwent treatment and thirteen served as controls. The authors report a measure of selective cooling called the intracranial-bladder temperature gradient, and make the observation that it did not differ significantly between groups. Finally no mortality benefit was noted, as six and four patients died in the treatment and control groups, respectively. Certainly, the study was underpowered to detect changes in mortality, but it is notable that externally applied cooling did not result in significant differences in regional temperature gradients.

Qui and colleagues[32] performed a larger trial using a cooling cap and neckband among patients with traumatic brain injury. They examined 90 patients who presented with severe TBI (GCS <8) and prompt CT diagnosis of brain injury (<4.5 hours). Both groups had similar demographics, admission GCS, pupil examination, admission intracranial pressure (ICP), rate of craniotomy and findings on head CT (intracranial hematoma, diffuse brain injury and contusions and others). All patients underwent standard care for severe TBI in accordance with American Association of Neurological Surgeon guidelines. In addition to standard TBI care, 45 patients underwent selective brain cooling by means of a cooling cap (with circulating water at 4°C) and a cooling neckband.

The authors note favorable results. They were able to achieve and maintain mildly hypothermic parenchymal temperatures of 33-35°C (after four hours of cooling on

average) for three days. Core systemic temperatures were maintained in the normothermic range during the intervention period. The average intracranial pressure in the intervention group at 24, 48 and 72 h after injury were significantly lower than that of the control group. (19.14±2.33, 19.72±1.73 and 17.29±2.07 mmHg, versus 23.41±2.51, 20.97±1.86, and 20.13±1.87 mmHg, respectively, p<0.01). At six month follow-up, however, there were no significant differences in Glasgow Outcome Scale (GOS) between the cooled group and the control group. There were no major differences in adverse outcomes. These results stand in contrast to other studies that have failed to show efficacy for external selective cooling strategies in adults.

Surface cooling after hemicraniectomy – Surface cooling has also been utilized in the setting of hemicraniectomy. The removal of bone and durotomy facilitate heat transfer from the brain parenchyma, allowing for more effective neural cooling. Prandini et al.[33], using a rabbitt model of middle cerebral artery occlusion, demonstrated that mild regional hypothermia induced by craniectomy and ice pack surface cooling reduced stroke volume after sacrifice. Forte et al., applied this cooling technique to human subjects who had undergone hemicraniectomy for varying indications. 23 patients were enrolled in the study and they demonstrated the ability to induce sustained cooling of brain parenchyma from a mean of 37.1°C to 35.2°C (p<0.0001) utilizing surface ice packs overlaying the craniectomy defect. Additionally, regional cooling in these patients induced a decrease in intracranial pressure (28 mmHg to 13 mmHg).

Invasive methods of CNS cooling

In contrast to non-invasive methods, invasive techniques have far fewer human trials. It is not entirely fair to describe the field as in its infancy however, as enthusiasm began as early as the 1960s and 1970s; unfortunately, early enthusiasm did not persist. Invasive techniques likely represent an understudied approach to selective hypothermia. Nevertheless, several investigations are worthy of discussion. We divide this section into selective cooling methods utilizing the cold perfusion via the cerebral vasculature and those that utilizing conductive and convective transfers of heat from the various intracranial compartments.

Vascular cerebral cooling methods

The cerebral vasculature offers an attractive route to achieve selective brain cooling by nature of its dense arborization and diffuse distribution. Efforts have been focused mostly on injections of cooled saline or blood into the extracranial internal carotid artery. Cooling of the brain beyond the arterial territory accessed relies on the collateral circulation of the communicating arteries in the Circle of Willis. We also present techniques of retrograde venous perfusion and extraluminal cooling of the extracranial carotid artery.

Extraluminal anterograde cerebral perfusion – Wei et al.[34] used a cooling cuff with circulating cold water that encased the common carotid artery to induce selective cooling of the cerebral hemispheres in a rat model. Using intraparenchymal temperature monitors they demonstrated the ability to selectively decrease brain temperature by 3°C within 20 minutes. They applied this cooling method for 90 minutes, beginning 30 minutes after middle cerebral artery occlusion, and found a significant decrease in histologic infarct size at 24 hours post-ischemia.

Intraluminal anterograde cerebral perfusion – Cheng and colleagues[35] used a rat model to demonstrate that localized arterial infusion of cold solution can decrease infarct size among rats subjected to hypoxia ischemia insult. Schwartz and colleagues[36] extended these findings in a baboon model. After induction of general anesthesia in twelve baboons, the right carotid and right femoral artery were occlusively cannulated. In a closed circuit loop, blood was drawn from the femoral, chilled in a water bath, and infused in the right internal carotid artery. The authors demonstrate that both right and left-brain temperature cooled as a result. Temperature in the right (R) cerebrum decreased from 34°C to 18.5±1.1°C. At the same time, left cerebral temperature decreased to 20.7±1.6°C. After half an hour of cerebral hypothermia, esophageal temperature decreased from 35.1±2.3°C to 34.2±2.2°C, p<0.05. There was no change in R brain blood flow. Finally, Neimark and colleagues[37] created a quantitative brain cooling model and assessed the theoretical temperature changes in response to intracarotid cold saline infusion, a cooling cap, or a combination of both. The authors confirmed the inability of cooling caps alone to achieve cold temperatures deep within brain parenchyma, a finding that aligns with other research we have discussed.

Wolfson et al.[38] gave 0°C saline at 10 mL/kg/min for 5 min to nine dogs immediately after cardiac arrest (VF), with another 10 mL/kg halfway through the arrest period. The dogs were resuscitated after 20, 30, or 40 min. Brain temperature fell to 20°C and esophageal temperature to 33°C. Body warming was not used. All of the dogs survived without brain damage, but those subjected to 30 and 40 min of circulatory arrest had spinal cord damage. Bacalzo and Wolfson[39] experimented with seven baboons placing ice packs around their heads, inducing 30 min of cardiac arrest and, after 3 min, administering a right carotid flush with 0°C saline at 10 mL/kg/min for 6 min. Right brain temperature fell to 16°C and left brain

temperature to 21°C (i.e., there was a lateral temperature gradient). Body warming was not used and esophageal temperature fell to 33°C. The baboons survived without detectable gross neurological damage.

Retrograde jugular venous cooling – Extrapolating from cardiac surgical experiences with retrograde cerebral perfusion, Wen et al.[40] used a 4°C retrograde saline flush into the external jugular vein to induce selective brain cooling. This method produced an immediate decline in intraparenchymal temperatures from 35.5°C to 34.5°C, lasting 20 minutes, in a rat model.

Selective cooling of the brain through the cerebral vascular has been shown to be effective in numerous models. It is possible to obtain bihemispheric cooling using only unilateral cooling methods. A major limitation of this method is the risk of vascular injury and resultant ischemia associated with direct carotid puncture. Common variations in the Circle of Willis may limit the ability to cool numerous vascular distributions. Finally, in situations were cerebral perfusion is compromised – focally, as in ischemic strokes, or globally, as in TBI – this cooling approach would be least effective in most compromised areas of brain. Differences in vascular anatomy in animal models may limit the generalizability of these studies to human populations.

Compartmental cooling

Different intracranial compartments are commonly accessed in clinical practice by mildly invasive methods for monitoring of ICP and for CSF drainage. Selective cooling of the brain may be achieved by conductive or convective methods through these compartments. We discuss here selective cooling strategies using the epidural, subdural, subarachnoid and intraventricular spaces.

Epidural cooling – Cheng et al.[41] used continuous epidural irrigation with chilled saline administered via burr holes to convectively cool the brain. In their porcine model, they achieved epidural temperatures of 13°C, subdural temperatures of 19°C and parenchymal temperatures of 28°C. Induction of local hypothermia took 5 minutes from initiation of the chilled saline drip and was maintained for 6 hours without difficulty. Distant brain temperatures were not measured.

King et al.[42] evaluated the effects on brain temperature of a cooling device called the ChillerPad applied to the dura in a non-human primate TBI model using controlled cortical impact (CCI). The cortical surface was cooled to approximately 15°C and maintained at that level for 24 hours followed by rewarming over about 10 hours. Brain temperatures fell to 34 to 35°C at a depth of 15 mm at the cortical gray/white interface and to 28 to 32°C at 10 mm. Cooling rapidly diminished at points distant from the cooling pad.

Subdural cooling – Using a cat model, Noguchi et al.[43] induced local brain cooling by infusing the subdural space with 20°C saline entering via a parietal burr hole and exiting through an orbitotomy. Rectal temperatures remained at 37°C, surface parenchymal temperature (5 mm depth) cooled to 33°C, while deep parenchymal (15 mm depth) cooled to 35°C. This mode of local brain hypothermia decreased cortical edema and enabled improved somatosensory evoked potential (SEP) amplitudes as compared to controls in middle cerebral artery occlusion induced ischemia.

Subarachnoid – In 1970, Sourek and Tranvnicek[44] reported their experience with 23 patients suffering from intractable epilepsy who underwent subarachnoid catheter irrigation of 0°C saline. In this cohort, subarachnoid irrigation produced local decreases in brain surface temperatures ranging from 20-27°C. Deep brain temperatures increased 2°C per 10 mm from the cortex. Cooling took between 20-60 minutes and was associated with a 1-2°C drop in rectal temperature. There was one death 6 weeks post-op from bilateral intracerebral hemorrhage (which they postulated to be unrelated to the cooling procedure), five cases of transient weakness and one case of persistent facial weakness at six month follow-up. They do not report the type or location of temperature measurements, nor do they report distant brain temperatures.

Intraoperative direct lavage – Recently, Prandini et al.[45] utilized intra-operative direct cold lavage to induce local subcortical hypothermia in patients who required temporary clipping during middle cerebral artery aneurysm surgery. Their protocol involved epidural lavage with an 11°C saline-papverine solution prior to durotomy, followed by subarachnoid lavage until local parenchymal temperature, measured 15 mm subcortically, was 29.5°C-30.5°C. In their 68 consecutive patients, they convincingly demonstrate the efficacy of this approach for achieving local hypothermia while maintaining systemic normothermia. Moreover, they demonstrate the safety of this technique, in the 68 patients there were no intraoperative ruptures and no post-operative neurological decline.

Intraventricular – In the 1960s and 1970s there were a series of attempts at inducing selective cerebral hypothermia using intraventricular infusion of chilled fluids.

Costal et al.[46] report their experience with 20 dogs that they subjected to intraventricular cooling with various influent and effluent sites. They infused 5°C saline at an average rate of 7-10 cc/min for 2-7 hours, maintaining ICPs between 1-5 cmH$_2$O and measuring parenchymal temperatures 1-1.5 cm from cortex. They demonstrated sustained parenchymal temperatures as low as 13°C. They also demonstrated the relative thermal separation between the supra- and infra-tentorial compart-

ments, comparing cerebellar and cerebral temperatures during fluid flow directed from the lateral ventricle to the cisterna magna to fluid flow from the ipsilateral to the contralateral lateral ventricle. Many of their dogs showed evidence of systemic cooling as well as cerebral hypothermia, but a significant cortical-systemic gradient was typically evident. Adverse events (including deaths) were noted when there was obstruction of the CSF pathways during infusion.

Tokuoka et al.[47] report similar results in 20 dogs cooled by intraventricular infusions utilizing various influent and effluent sites. Additionally, they report their experience in 3 human psychiatric patients upon whom they performed cold intraventricular irrigation using 8°C saline. Influent site was the lateral ventricle in all cases; effluent site was the cisterna magna in two cases and the contralateral lateral ventricle in the third case. There were no reported complications from the intraventricular cooling and they report improved psychiatric states subsequent to cooling (one "became docile" and the other two were "alleviated from violent attacks").

Selker[48], also using dogs, performed suboccipital craniotomies and vermian resection to enable irrigation of the floor of the fourth ventricle with 4°C saline. This procedure enabled cooling of the brainstem to 19°C. In a minority of cases, transient respiratory alterations were observed at the onset of irrigation.

Compartmental cooling strategies have been shown to be effective in numerous animal models. These results are easily generalizable to human populations. While effective in locally cooling the brain, epidural cooling strategies may be restricted to isolated regions of the brain by virtue of epidural adhesions to the cranium. Subdural cooling offers a strategy that may affect a greater area of brain than epidural cooling. Subarachnoid cooling most directly cools the cortical surface. Additionally, subarachnoid cooling may globally impact the cerebral vasculature that resides in this space. Intraventricular cooling can induce profound decreases in brain temperature, however also carries the attendant risk of iatrogenic hydrocephalus. Compartmental cooling strategies carry additional risks of infection and intracranial bleeding.

Final remarks

The beneficial role of hypothermia after neurological insult or injury is a well established and enticing concept. However, there are risks with systemic cooling, which have limited its application. In contrast, the role of selective therapeutic hypothermia offers promise in reaping the benefits of therapeutic hypothermia, while avoiding the risks of whole body cooling and rewarming. Human research in selective hypothermia is limited to non-invasive cooling methods. While non-invasive methods offer many advantages, including easy and prompt administration, the field is limited in the ability to cool the deep parenchyma of the brain, and trials on adult humans have been disappointing. Neonates have shown benefit through non-invasive strategies, though likely their unique anatomy prevents generalization of these findings. The use of surface cooling in the setting of hemicraniectomy is deserving of further investigation and may prove beneficial in the appropriate settings (e.g. malignant ischemic stroke). In contrast, invasive methods of hypothermia, a field once popular, are in need of a revival. Invasive techniques have the potential to provide rapid, reliable, and selective brain cooling. Animal experiments have yielded encouraging results using various invasive methods of selective brain cooling. Human data, however, remains largely absent. Further human experiments and trials are warranted. Possibilities for future trials are numerous and range from simple and accessible experiments, such as transcutaneous cooling in patients with decompressive craniectomies, to more complex interventions, such as intraluminal arterial cooling. Moreover, selective brain cooling techniques have potential applicability to a variety of disease processes, including traumatic brain injury, status epilepticus, ischemic stroke, global cerebral ischemia/hypoperfusion, intracerebral hemorrhage and subarachnoid hemorrhage.

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