Therapeutic hypothermia in stroke: Quo Vadis?

Neuroprotection continues to be an elusive target despite numerous candidates.[1] For decades, multiple promising compounds and strategies failed to translate encouraging experimental results into meaningful clinical benefits. Many therapies are still undergoing testing, while others are being refined or developed. This is particularly the case for neuroprotection in the acute ischemic stroke setting. The advent of endovascular thrombectomy has revived interest in neuroprotection. It awaits testing of when it should be administered: before/during/or after, fast and complete reperfusion.[2] The ESCAPE-NA1 trial (NCT02930018), which has just completed recruitment, and PROOF (NCT03500939) trial will be the first to test promising neuroprotectants coupled with endovascular reperfusion.

Therapeutic hypothermia (TH) exceeds all other neuroprotective therapies in the wealth of robust evidence supporting its efficacy.[3] Whether in experimental studies or at the bedside for postcardiac arrest patients or neonates with hypoxic-ischemic encephalopathy, TH demonstrates potent neuroprotective effects.[4,5] Unfortunately, the benefits of TH have not been shown in ischemic stroke patients despite multiple trials.[6] These trials have been criticized for the slow induction of TH after stroke onset; the use of various methods to induce systemic hypothermia, applied for different durations; and – most importantly – the inclusion of patients with varying volumes of infarct and reperfusion therapies. ICTuS 2/3 and, most recently, the EuroHYP-1 study had to be prematurely terminated due to slow recruitment (enrolled 120 and 98 of planned 1,600 and 1,500 patients, respectively), indicating low feasibility of the applied whole-body cooling in awake stroke patients.[7,8] Both trials reported no benefit of TH compared to controls in improving 90-day functional outcome but also no significant differences in serious adverse events between the two trial arms. Pneumonia rates in TH patients (19% and 18%) trended to be twice as high compared to controls (11% and 4%, respectively).

These results prompted the search for better delivery methods to harness the benefits of TH while avoiding the potentially harmful effects of whole-body cooling and – at the same time – enhancing feasibility. Selective TH is promising to achieve these goals by targeting the brain, even the ischemic hemisphere, while sparing the rest of the body.[9] Promising approaches include transnasal cooling, intra-arterial carotid infusion of chilled saline (open-loop cooling), closed-loop cooling using dual-lumen balloons and extracorporeal blood cooling, and transvenous retrograde cooling. Despite the quality evidence supporting selective TH from experimental studies, there are limited human studies.[10,11] This issue represents an opportunity to inform the design of future trials of selective TH to avoid the pitfalls of systemic TH trials. Selective TH needs to be applied as soon as possible, ideally before reperfusion, but at least at the time of reperfusion or shortly after. It is paramount that these therapies can be smoothly incorporated into the workflow of acute stroke therapies without introducing reperfusion delays. Treatments should achieve rapid induction of brain cooling and maintain that for sufficient time, possibly hours. This may require combining more than one approach to facilitate cooling for longer durations, for example, hypothermia induction via an endovascular approach followed by a noninvasive maintenance approach. Future trials should aim to target patient population that is likely to benefit from TH. Those could include patients with a large ischemic core at baseline, those with inadequate collaterals, older patients, and those with expected delays to reperfusion, for example, transferred from distant centers.[12]

This special issue of *Brain Circulation* attempts to highlight some of the opportunities and challenges of selective TH of the brain, mainly in the ischemic stroke setting. These articles highlight science and reviews from investigators who are actively working in the field of TH. The evidence for TH in stroke setting is discussed with attention to systemic versus selective approaches[13,14] and the methods to achieve that. The articles by Mattingly and Lownie and Cattaneo and Meckel[15,16] discuss different strategies for attaining intra-arterial selective TH via closed-loop cooling. This approach has the advantage of avoiding the volume overload from the infusion of chilled saline. However, the setting for the closed-loop system and the incorporation of these systems into stroke care pathway remains to be determined. Open-loop, intra-arterial infusion of chilled saline can be easily incorporated into the workflow of endovascular thrombectomy procedures. However, the article by Merrill *et al*.[17] shows that significant warming occurs when chilled saline passes through the tubes and then via uninsulated catheters into the carotid artery when it warms further as it mixes with the blood. The infusate volume required to produce brain cooling and the resulting hemodilution are also factors to be considered when employing this approach. Transvenous selective retrograde brain cooling is another

innovative approach that is promising to achieve rapid deep hypothermia.[18] The target brain temperature needed to achieve neuroprotection is not well defined. Lyden *et al*.[19] discuss moderate hypothermia (~33°C) which appears to provide better neuroprotection compared to mild hypothermia (35°C–37°C). This target temperature might be challenging to reach with noninvasive cooling methods. The investigators also perform some sample size calculations to show that a large clinical trial would be needed to demonstrate an outcome difference between mild and moderate hypothermia. Chen *et al*.[20] propose using high-quality primate models, for example, cynomolgus macaques, before large-scale, randomized controlled trials are undertaken. Such studies could determine the safety and efficacy of various methods and target temperatures for TH using hyperacute imaging, novel biomarkers,[21] and subsequent investigation of functional recovery. Finally, a word of caution regarding TH by Kalisvaart *et al*.[22] summarizes the current evidence regarding the potential effects of various depths and durations of hypothermia on postinjury brain plasticity.

These articles do not cover all aspects related to TH. However, they raise important questions and attempt to solve important challenges relevant to all researchers interested in TH application in stroke setting. They will hopefully inform the design of future studies. Moreover, this work could facilitate the networking of groups that are interested in or actively working in the field of TH. The idea of this issue stemmed from such a networking event that included many of these issue contributors who attended the 1st Selective Hypothermia Symposium, which took place at the University of Calgary in March 2019. We hope that this issue will be an excellent opportunity for future collaboration and to keep the discussions ongoing.

Less than a decade ago, investigators struggled to show the benefits of endovascular thrombectomy in acute ischemic stroke. Subsequently, a flurry of positive trials came forward. What it took to achieve this was for investigators to select and enroll the optimal patient population and treat them fast, using safe and effective devices. We hope that neuroprotection trials will learn from the thrombectomy experience and follow the same path toward helping stroke patients.

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