

Regional cerebral infusion for acute ischemic stroke

Acute ischemic stroke (AIS) is a leading cause of death and disability, worldwide. Clinical investigation has yielded promising treatment options for AIS, but the transition from benchtop to bedside has proven difficult. At present, recanalization using recombinant tissue plasminogen activator (tPA) is the best accepted and most widely available reperfusion method. However, a therapeutic window of 4.5 h from symptom onset prevents the vast majority of AIS patients from receiving thrombolytic recanalization; recent evidence suggests that only 6%–8% of AIS patients actually receive tPA.^[1] As an alternative to tPA, mechanical thrombectomy (MT) has gained popularity in recent years but is typically only beneficial in patients with a large-vessel occlusion, and surgical candidacy requires perfusion imaging indicating a sufficiently large mismatch.^[2] In response to this lack of therapeutic options, hundreds of neuroprotective strategies have been investigated in the preclinical setting in hopes of finding new ways to improve outcomes in stroke patients to whom tPA or thrombectomy is not an option. After a half century of work, one neuroprotective strategy has separated itself from the rest, therapeutic hypothermia. Here, we introduce regional cerebral infusion (RCI), the most advanced and promising therapeutic hypothermia induction method.

RCI is a method of targeted cerebral hypothermia, wherein the ischemic region of the brain is cooled by perfusing chilled saline directly to the infarct site using an endovascular catheter. By isolating hypothermic efforts to the ischemic region, the brain can be cooled in a matter of minutes, and since RCI avoids cooling the whole body, the metabolic and hematologic drawbacks of hypothermia are avoided. In addition, since AIS is increasingly treated using endovascular techniques, RCI could be administered through the same catheter used for thrombectomy, making clinical implementation relatively simple and cost-effective.

Over the past 20 years, RCI has been extensively investigated in the preclinical and clinical settings. Ding *et al.* first described prereperfusion RCI in a landmark 2002 study.^[3] Before reperfusion, this group infused isotonic saline at 23°C or 37°C into the ischemic territory of rats with a transient middle cerebral artery occlusion. The rats receiving prereperfusion RCI demonstrated significantly increased cerebral blood flow, decreased infarct volumes, and improved neurologic outcomes. In a

follow-up comparative analysis, Ding *et al.* demonstrated that prereperfusion RCI allowed achievement of cerebral target temperatures much more effectively than systemic infusion was able to, and that this cooling translated to significantly smaller infarct volumes and augmented functional recovery.^[4] Then two other studies came to the same conclusion.^[5,6] Another study by Chen *et al.* also demonstrated a synergistic effect of regional cerebral infusion and low-dose Alb infusion in acute ischemic stroke.^[7] Through these experiments, the neuroprotective efficacy of RCI was established.

Following the success in rat models, the safety and efficacy of the RCI concept were evaluated in larger mammals. In a 2016 study, cold lactated Ringer's solution was infused into the middle cerebral artery of healthy Rhesus monkeys via RCI.^[8] Target temperatures were achieved within minutes, and no cerebral edema, vasospasm, or cerebrovascular reactivity were observed, thereby establishing RCI as a safe, effective cooling method in models more similar to humans [Table 1].

The next step toward clinical implementation of RCI was taken by our group in a 2016 pilot study.^[9] In this clinical trial of 26 patients with AIS, a microcatheter was advanced through the thrombus and ice-cold saline was perfused before stent retrieval and continued for several minutes following recanalization [Figure 1]. The local temperature of ischemic cerebral tissue decreased by an estimated 2°C or greater, and there were no appreciated side effects of cold infusion. In this way, we established the safety of RCI in humans. We then set out to investigate its cooling efficacy; in a 2018 trial, 45/113 patients received RCI plus MT, while remaining subjects received MT alone.^[10] In patients who received RCI and MT, infarct volumes

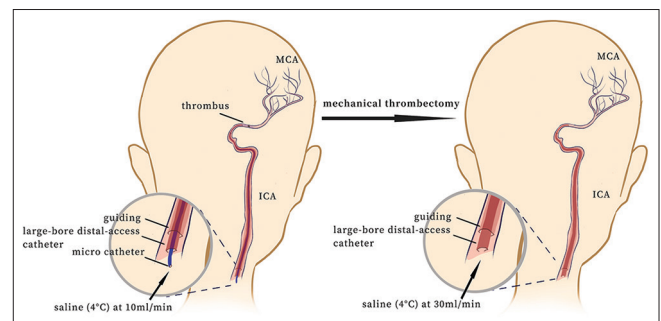


Figure 1: Sketch map of the regional cerebral infusion procedure in patients

Table 1: The effect of regional cerebral infusion in preclinical experiments

Author's name/year of publication	tMCAO (h)	Model	IACI pre- or post-reperfusion	Infusate/solution temperature (°C)	Duration (min)	Target temperature (°C)	Time to reach target temperature	Infarct volume compared to control groups (%)	Functional outcome compared to controls
Ding <i>et al.</i> /2002 ^[3]	2	Rodent	Prereperfusion	Saline/22	3-4	32-33	3-4	-65	Improved
	2	Rodent	Prereperfusion	Saline/37	3-4	37	3-4	-82	Improved
Ding <i>et al.</i> /2004 ^[4]	3	Rodent	Prereperfusion	Saline/20	10	33.4-33.9	≤10	-93	Improved
Ji <i>et al.</i> /2012 ^[5]	3	Rodent	Postreperfusion	Saline/10	3×10	34.6	60-70	-32	Improved
	3	Rodent	Postreperfusion	Saline/10	30	34.6	20-25	-33	Improved
Ji <i>et al.</i> /2012 ^[6]	2	Rodent	Postreperfusion	Saline/10	20	33-34	Unknown	-56	Improved
	2 + 1	Rodent	Postreperfusion reperfusion	Saline/10	20	33-34	Unknown	-42	Improved
	2 + 2	Rodent	Postreperfusion reperfusion	Saline/10	20	33-34	Unknown	-32	Improved
Chen <i>et al.</i> /2013 ^[7]	2	Rodent	Prereperfusion	Saline with human albumin/0	45	30.5	3	-67	Improved
	2	Rodent	Prereperfusion	saline	45	30.5	3	-32	Improved
Wang <i>et al.</i> /2016 ^{[8]*}	-	Rhesus monkey	-	lactated ringer's solution/10	20	<35	10	-	-

*This study used healthy rhesus monkeys without MCAO mainly to describe the feasibility and safety of IACI in large animal models. MCAO: Middle artery occlusion, tMCAO: Transient MCAO

Table 2: The effect of regional cerebral infusion in aforementioned clinical trials

Author's name/year of publication	Time from symptoms onset	Infusate/solution temperature (°C)	Duration (min)	Infarct volume compared to control groups (%)	Functional outcome compared to controls
Chen <i>et al.</i> /2016 ^[9]	<8 h	4	15	-	-
Wu <i>et al.</i> /2019 ^[10]	<6 h	4	15	18	51.1% vs. 41.2%

were significantly reduced compared to MT alone, and the rate of complications was no different between the groups; the cooling efficacy of RCI in humans is now established as well. To our knowledge, these studies are the first to establish an effective neuroprotective adjunct to recanalization in humans, which represents a massive step forward in stroke care [Table 2]. Based on these encouraging results of these studies, a randomized clinical trial is ongoing to further assess the efficacy of the RIC plus MT for AIS patients with large-vessel occlusion (ClinicalTrials.gov number: NCT03163459). As of November 30, 2019, 46 patients have been randomly assigned.

Although RCI has made great strides over the past two decades, there is still a long way to go. Previous investigations have utilized a wide variety of target temperatures, durations of hypothermia, and induction times, which make it difficult to meaningfully compare data from different studies. In addition, there is a potential for harm if hypothermia is too deep or if infusion volumes are too large, so the depth, duration, and therapeutic window all require optimization if RCI is to gain clinical acceptance going forward.^[11] Future investigations should focus on optimization of these variables as they likely play a significant role in the degree of benefit that RCI would provide to patients.

Another potential avenue of investigation is the combination of RCI with other neuroprotective strategies. In particular, RCI allows for co-administration of neuroprotective drugs directly to the infarct site, which maximizes local drug concentrations while avoiding their dose-dependent systemic side effects. Indeed, several recent investigations have demonstrated a synergistic neuroprotection when RCI is co-administered with magnesium sulfate^[12] or a human albumin solution.^[7] This concept provides a multitude of new therapeutic opportunities and opens up a world of possibilities for stroke clinicians.

The neuroprotective benefits of RCI have been well established in preclinical models, and clinical trials have recently demonstrated to safety and feasibility of RCI in an ischemic stroke patient. Thus, RCI holds significant promise for future stroke treatment and rehabilitation. Moreover, the technical skills and equipment required for the procedure are no different from that of a thrombectomy; cost and training are not hurdles to clinical implementation. We sincerely appreciate the benchtop and clinical work that has been done so far, but future investigations are warranted; large, randomized clinical trials are required for any widespread clinical acceptance to occur. Given the cost-effective and robust neuroprotective efficacy that

RCI provides, it may fill the void of recommended neuroprotective methods in AIS and benefit patients all over the world.

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Conflicts of interest

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