Local endovascular infusion and hypothermia in stroke therapy: A systematic review

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Abstract:

Ischemic stroke is a leading cause of death and disability worldwide, but there are no effective, widely applicable stroke therapies. Systemic hypothermia is an international mainstay of postcardiac arrest care, and the neuroprotective benefits of systemic hypothermia following cerebral ischemia have been proven in clinical trials, but logistical issues hinder clinical acceptance. As a novel solution to these logistical issues, the application of local endovascular infusion of cold saline directly to the infarct site using a microcatheter has been put forth. In small animal models, the procedure has shown incredible neuroprotective promise on the biochemical, structural, and functional levels, and preliminary trials in large animals and humans have been similarly encouraging. In addition, the procedure would be relatively cost-effective and widely applicable. The administration of local endovascular hypothermia in humans is relatively simple, as this is a normal part of endovascular intervention for neuroendovascular surgeons. Therefore, it is expected that this new therapy could easily be added to an angiography suite. However, the neuroprotective efficacy in humans has yet to be determined, which is an end goal of researchers in the field. Given the potentially massive benefits, ease of induction, and cost-effective nature, it is likely that local endovascular hypothermia will become an integral part of endovascular treatment following ischemic stroke. This review outlines relevant research, discusses neuroprotective mechanisms, and discusses possibilities for future directions.

Keywords:

Endovascular stroke therapy, local endovascular infusion, local hypothermia

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Introduction

Therapeutic hypothermia (TH) is one of the best studied and most highly effective forms of ischemia protection available today. Induced hypothermia is an international staple of care after cardiac arrest, and the practice has started to gain attention as a theoretical neuroprotective strategy after ischemic stroke.[1] Multiple groups have demonstrated the remarkable benefit of mild-to-moderate hypothermia (30°C–34°C) in limiting the damage of focal and global ischemia in animal models and clinical studies.[2-4] Until recently, the primary focus of these investigations had focused on whole-body cooling. Whole-body cooling by surface and endovascular methods has been widely applied in studies of acute ischemic stroke therapy,[5,6] but while safe and effective, its implementation into clinical practice has been limited by logistical issues and severe side effects (see "Whole-Body Cooling" below).

In response to the drawbacks of whole-body cooling, local endovascular infusion (LEVI) of cold saline directly into the infarct site has garnered attention as a novel, effective way to maximize the benefits of cerebral hypothermia while avoiding the detrimental side effects of whole-body cooling. With LEVI, a microcatheter is threaded directly to the infarct site, and then, cold saline is perfused into the ischemic region for a

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variable length of time (usually 5–30 min),[7] which allows for more rapid achievement of target temperatures and permits selectivity in hypothermia application. Since the cold saline is only perfused into the ischemic area, the volume needed to attain target temperatures is negligible compared to total blood volume, which translates to minimal change in body temperature, thereby eliminating the adverse effects of whole-body cooling. Logistically, the implementation of LEVI into clinical practice would be a smooth transition, as image-guided microcatheter placement is a daily practice for most neurointerventionalists.[8]

Whole-Body Cooling

The use of whole-body TH to preserve ischemic tissues has been investigated extensively but largely in the context of cardiac arrest, where it is a standard of care.[2] Sentinel studies on the topic utilized "surface cooling" methods – cooling using cold blankets or ice packs applied to the skin – and later trials utilized invasive cooling methods, such as systemic infusion of cold fluids or the placement of central venous cooling catheters. Likewise, the best-known investigations into TH in stroke feature whole-body cooling.[5,6,9,10] Surface cooling methods are easy to use and permit early treatment initiation, which makes them an attractive option. Unfortunately, whole-body cooling creates a number of serious complications. Chiefly, the body responds to cooling with shivering and dermal vasoconstriction, which combats effective progression to target temperatures; whole-body cooling frequently requires 3–7 h to reach optimal degrees of cooling, which is well outside the 2–3-h window in which hypothermia is maximally protective.[11-13] Shivering also raises intracranial pressure and requires the use of several pharmacological agents to inhibit these effects along with skin warming to address physical discomfort.[14,15] Whole-body cooling also increases the risk of pneumonia, which was the basis for the American Heart Association's recommendation to induce hypothermia after stroke only in the context of clinical trials.[16] The practice also increases the risk of shear-induced platelet aggregation and a variety of cardiovascular, renal, and metabolic complications.[5,15,17-19] However, since the entire body is ischemic during cardiac arrest, whole-body cooling is necessary to preserve vital functions, which makes these problems intrinsic to the therapy, but a small price to pay.

Benefits of Local Endovascular Infusion over Systemic Infusion

While whole-body cooling is necessary in the context of cardiac arrest, only a small amount of cerebral tissue needs to be preserved in the context of ischemic stroke, which renders the adverse effects of whole-body cooling unnecessary and extrinsic to the problem at hand. In addition, given the brain's vulnerability to ischemic damage, any delay in progression to target temperatures is unacceptable. In response to the detriments of whole-body cooling for ischemic stroke therapy, LEVI of cold saline directly into the infarct site using a microcatheter has been put forth. LEVI has been tested in animal models of stroke both before and after reperfusion. Compared to whole-body cooling, which requires hypothermia to spread into the ischemic region slowly, LEVI reduces infarct temperatures by perfusing ice-cold saline directly to the ischemic region, a much more effective method of hypothermia induction. In a murine model of ischemic stroke, prereperfusion LEVI was able to achieve cerebral hypothermia in <10 min[20,21] (23°C saline infused at 2 mL/min for 3–4 min), and postreperfusion LEVI took just over 20 min to reduce brain temperature below 35°C (infusion of 10°C saline at 0.25 mL/min).[22] Prereperfusion flushing was first proposed by Ding *et al*. in 2002, when using LEVI before resolving a 2-h middle cerebral artery occlusion in rats, which produced a 65% reduction in infarct volumes and 61% reduction in leukocyte infiltration.[23] Prereperfusion LEVI has since been shown to reduce infarct volumes by 75%–90%[21,23] and significantly conserve motor function both hours and weeks after stroke.[21,23] Postreperfusion LEVI has also been applied to some studies using a catheter that was introduced into the internal carotid artery after blood flow to the ischemic territory had been reestablished. Both infarct volume reduction and functional recovery were observed in postreperfusion LEVI, and the effect seemed to be most pronounced if the infusion was started immediately after reperfusion, but these improvements were not as pronounced as those found with prereperfusion LEVI.[22]

Although the majority of experimental data on LEVI in stroke are based on rat models, the credibility,[24] safety, and efficacy[25] of LEVI have also been confirmed in large animals, such as swine[26] and Rhesus monkeys.[24,25] Importantly, the safety and feasibility of LEVI were recently verified in humans as well.[7,27] In 9 human patients with partially or completely treated cerebrovascular diseases undergoing diagnostic cerebral angiogram, Choi *et al*. demonstrated that 7°C LEVI at ~33 mL/min for 10–13 min was able to reduce the temperature of jugular venous blood (a proxy for brain temperature) by 0.84°C with a negligible effect on core body temperature or vital signs.[27] The group then utilized a mathematical model to evaluate their effect on brain parenchymal temperature itself, which estimated that their experiment dropped the perfused region by 2°C within 10 min.[28] These investigations proved that LEVI in acute ischemic stroke was feasible and safe and did not lead to any obvious complication. In another recent study, the temperature of ischemic cerebral tissue was decreased by at least

2°C during infusion of the cold solution while only mildly reducing systemic temperature (maximum 0.3°C) in all 26 patients involved.[7] However, while these investigations established that LEVI allows effective progression to target temperatures, the neuroprotective efficacy of LEVI has not yet been established in humans.

The mechanisms of LEVI-induced neuroprotection are largely the same as those of whole-body cooling. However, LEVI retains a few unique features that make it considerably more effective than global cooling. Chiefly, LEVI maximizes the rate of cooling. It is well accepted that "time is brain," which emphasizes that human nervous tissue is rapidly lost as the stroke progresses, such that rapid therapy is highly desirable. Although there is no consensus on the optimal treatment window for TH, most investigations on the topic identify treatment windows of minutes to 2–3 h after reperfusion.[11-13] Given that surface cooling methods frequently take 3–7 h to reach target temperatures,[29] the brain may have already been unsalvageable by the time effective temperatures are reached. In contrast, LEVI can establish target temperatures in a matter of minutes[27] in experimental models; in a 300-g localized cerebral infarct, LEVI attained target temperatures 30-times faster than classic surface cooling and 10–20 times faster than systemic infusion of cold saline into the inferior vena cava.[30] The time saved using LEVI translates to superior degrees of neuroprotection and an improved quality of life for ischemic stroke patients.

Second, LEVI washes out harmful metabolic products created during ischemia. Ischemic conditions induce production of vasodilatory metabolites such as lactate, prostaglandins, and carbon dioxide, which trigger excessive vasodilation once perfusion is restored.[31] Literature suggests that this postischemic hyperperfusion is associated with edema formation, larger infarcts, and early death.[32,33] In addition to the neuroprotective effects of hypothermia in general, LEVI washes out these vasodilatory metabolites, which minimizes the extent of hyperperfusion-related injury.[34,35] As evidence of this mechanism, warm (37°C) saline LEVI has been shown to significantly reduce infarct volumes and improve functional recoveries compared to systemic infusion of warm saline.[23] In addition, prereperfusion flushing with cold and room temperature saline reduced expression of inflammatory markers in the peri-infarct vasculature compared to systemic infusion at either temperature.[23,36] Luan *et al*. showed that LEVI was able to reduce intercellular adhesion molecule-1 (ICAM-1) expression, and leukocyte infiltration to a significantly greater degree than local warm saline infusion or systemic cold saline infusion was able to, despite the fact that systemic cold infusion achieved comparable degrees of cerebral cooling.[36] Other studies have reported similar

conclusions.[37] These data imply that the neuroprotective advantages of LEVI over systemic infusion rely partially on its metabolite washout ability.

Moreover, LEVI allows for co-administration of neuroprotective drugs directly into the ischemic region along with hypothermic fluids, which maximizes local drug concentrations while minimizing systemic drug concentrations, thereby circumventing dose-dependent systemic side effects.[38] Song *et al*. found that LEVI of a magnesium sulfate solution at 15°C caused a 65% reduction in infarct volumes compared to sham groups, and the lowest brain water content and the greatest functional recovery of all groups that were tested.[39] Similar results were found following LEVI of a 20% human albumin solution cooled to 0°C[40] and LEVI of erythropoietin.[41] In addition, LEVI can aid in drug permeation into the brain parenchyma. A microcatheter can be used to transiently occlude any residual blood flow to the ischemic region while simultaneously infusing neuroprotective drugs. In a study by Woitzik and Schilling, a microcatheter was used to transiently occlude cerebral vessels before local infusion of MK-801 (an N-methyl-D-aspartate receptor antagonist, neuroprotective agent). This method resulted in 30% smaller infarct volumes at 24 h after infusion when compared to systemic infusion of MK-801.[38] While LEVI with neuroprotective drugs has never been tested in conjunction with microcatheter-based vessel occlusion, it is possible that the combination could yield synergistic benefits in stroke therapy. Moreover, the Woitzik study emphasizes the potential for LEVI to be creatively utilized to accomplish goals that would otherwise be unattainable.

Despite recent milestones in LEVI testing, several systematic obstacles have hindered widespread acceptance. The majority of LEVI studies have used rat models, but rats have been widely criticized for their poor translatability to clinical practice.[42] Furthermore, hypothermia-based investigations vary in animal model, animal age, duration of ischemia, duration of hypothermia, depth of hypothermia, method of hypothermia induction, and rate of cooling, all of which have consistently been shown to play critical roles in the efficacy of TH treatments. Given that stroke accounts for 9% of deaths worldwide and ~25% of stroke survivors are permanently disabled,[43] such a promising therapy is in serious need of further exploration.

Hypothermia-Induced Neuroprotective Mechanisms

Hypothermia by any mechanism affects multiple steps in several parallel pathways of hypoxia-induced brain injury. Hypothermia primarily exerts its neuroprotective

effects by slowing essential metabolic processes while preserving life, which subsequently attenuates pathways involved in excitotoxicity, free radical production, inflammation, edema, and apoptosis.[44,45]

When oxygen supply ceases during ischemia, neurons are unable to generate high-energy metabolites, which prohibits effective maintenance of ion gradients, thereby leading to increased intracellular calcium levels, increased glutamate release and excitotoxicity, cytotoxic and vasogenic edema, inflammation, and apoptosis.[44] Hypothermia combats this cascade at several points. Hypothermia preserves ATP levels, which maintains ion gradients, limits calcium influx, and decreases extracellular glutamate levels, all of which prevent intracellular calcium accumulation–excitotoxicity.[46]

Although reperfusion is a logical goal in stroke therapy, it is associated with negative consequences of its own. In the absence of oxygen, Ca^{2+} influx prompts the release of pro-inflammatory mediators from microglia, which initiates ischemia/reperfusion injury. These mediators (leukotrienes, interleukin-2β, interleukin-6, nitric oxide, and tumor necrosis factor-α)[47] increase leukocyte extravasation into brain parenchyma[48,49] and expression of matrix metalloproteinase-2 (MMP-2) and MMP-9, which contribute to vasogenic edema by damaging the blood–brain barrier.[50] Once leukocytes enter the brain tissue, they produce reactive oxygen species and pro-inflammatory factors of their own, thereby creating a vicious cycle of brain injury, inflammation, and blood–brain barrier breakdown. TH is able to confer anti-inflammatory neuroprotection by reducing the secretion of pro-inflammatory cytokines and inflammatory mediators (reactive oxygen and nitrogen species, E-selectin, and high mobility group box-1 protein).[51] Hypothermia can also prevent leukocyte extravasation by reducing endothelial expression of ICAM-1.[30,36] At the molecular level, hypothermia has been shown to suppress the pro-inflammatory transcription factor nuclear factor-kappa B and increase the expression of Hsp70, which aids in neuroprotection. In addition to reducing poststroke inflammation, hypothermia has been shown to reduce vasogenic edema after an ischemic stroke; an effect at least partially mediated by downregulation of MMP expression.[52] Hypothermia also reduces cytotoxic edema, largely through its ability to downregulate aquaporin-4 expression.[53-55]

The apoptotic pathway is activated when injured neurons activate regulatory proteins, which trigger the apoptotic process after ischemia.[51] Hypothermia has been shown to affect several aspects of apoptotic cell death in both the intrinsic (intracellular-mediated) and extrinsic (receptor-mediated) cell death pathways and ultimately prevents apoptosis after experimental stroke.[56] In the intrinsic pathway, cooling can alter the expression of Bcl-2 family members and reduce cytochrome c release.[57] Hypothermia can downregulate pro-apoptotic Bcl-2 family members (BID, BAX, BAD, etc.) and upregulate the anti-apoptotic Bcl-2 members (Bcl-2, Bcl-x, etc.) by a variety of mechanisms. The extrinsic apoptotic pathway is initiated by ligand binding to cell death receptors; the best studied being the FAS-ligand (FASL) and its receptor, FAS. Hypothermia affects this pathway at multiple levels. Cooling has been shown to suppress the expression of caspase-8, caspase-3, FAS, and FASL.[58]

Overall, there is compelling clinical evidence that prolonged mild-to-moderate cerebral hypothermia is neuroprotective when initiated within a few hours after hypoxia-ischemia and continued through the resolution of ischemia in term infants and adults.[59-61] The mechanisms underlying hypothermia-mediated neuroprotection are currently under investigation, and a common theme in literature on the topic is consensus on effects and uncertainty of mechanisms. While debate remains as to the precise mechanisms of hypothermia-mediated neuroprotection and their relative importance, virtually every investigation on the topic has found the same thing: when animals receive hypothermia after stroke, their brains are better protected on the biochemical, structural, and functional levels.

Future Studies and Clinical Perspective

The above studies have outlined the feasibility of using highly selective hypothermia induced by cerebral LEVI in acute stroke therapy. While the procedure is incredibly promising in theory, there are several hurdles toward clinical acceptance. Chiefly, study designs must become more homogenous. Variation in duration of ischemia, time of hypothermia onset, duration of hypothermia, animal model, animal age, and many other factors make side-by-side comparisons of results difficult and poorly translatable. In addition, most investigations have been conducted in rat models, so larger, more robust large animal studies are needed before clinical trials can be attempted. The ultimate hurdle is an investigation into the efficacy of LEVI in humans during acute ischemic stroke, which has yet to be determined.

There is also the potential for massive combination therapy in using LEVI along with recanalization strategies and neuroprotective "cocktails." Investigations using infusion of albumin, magnesium, and erythropoietin have all yielded impressive results, but this is just the tip of the iceberg. With the targeted application that LEVI provides, researchers are allowed an unparalleled freedom in the administration of neuroprotective agents

without the concern for systemic dose-dependent side effects. Therefore, in addition to brain cooling infusions, various combinations of neuroprotective agents could be regionally administered, and the ultimate neuroprotective concept of a "cocktail" could be devised.

Overall, LEVI provides a quick, effective method of neuroprotection, which the stroke community is in desperate need of. The procedure is also cost-effective and logistically simple, making the barriers to clinical acceptance very low. The strategy shows incredible promise, and if the stroke community continues to move toward clinical implementation, it could mean a massive impact in the lives of stroke patients across the world.

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There are no conflicts of interest.

References

1. Nielsen N, Wetterslev 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.

2. 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.

3. 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.

4. Huber M, Duan H, Chandra A, Li F, Wu L, Geng X, *et al*. Hypothermia in stroke therapy: Systemic versus local application. In: Zheng J, Zhou C, editors. Hypoxia and Human Disease. London, United Kingdom: InTech; 2017.

5. De Georgia MA, Krieger DW, Abou-Chebl A, Devlin TG, Jauss M, Davis SM, *et al.* Cooling for acute ischemic brain damage (COOL AID): A feasibility trial of endovascular cooling. Neurology 2004;63:312-7.

6. Lyden PD, Allgren RL, Ng K, Akins P, Meyer B, Al-Sanani F, *et al.* Intravascular cooling in the treatment of stroke (ICTuS): Early clinical experience. J Stroke Cerebrovasc Dis 2005;14:107-14.

7. 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.

8. Ringer AJ, Tomsick TA. Developments in endovascular therapy for acute ischemic stroke. Neurol Res 2002;24 Suppl 1:S43-6.

9. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, *et al.* Cooling for acute ischemic brain damage (cool aid): An open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001;32:1847-54.

10. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S, *et al.* Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): Final results. Stroke 2010;41:2265-70.

11. Zhang H, Tong ET. Neuroprotection of mild hypothermia beginning at different time intervals on cerebral ischemia/reperfusion injury. J Neurochem 2002;81:4.

12. Ji Y, Hu Y, Wu Y, Ji Z, Song W, Wang S, *et al.* Therapeutic time

13. window of hypothemia is broader than cerebral artery flushing in carotid saline infusion after transient focal ischemic stroke in rats. Neurol Res 2012;34:657-63.

13. Zhao H, Steinberg G. Limited therapeutic time windows of mild-to-moderate hypothermia in a focal ischemia model in rat. Stroke Res Treat 2011;2011:131834.

14. Jeon SB, Koh Y, Choi HA, Lee K. Critical care for patients with massive ischemic stroke. J Stroke 2014;16:146-60.

15. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186-202.

16. 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-e110.

17. Connolly JE, Boyd RJ, Calvin JW. The protective effect of hypothermia in cerebral ischemia: Experimental and clinical application by selective brain cooling in the human. Surgery 1962;52:15-24.

18. 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.

19. Zhang JN, Wood J, Bergeron AL, McBride L, Ball C, Yu Q, *et al.* Effects of low temperature on shear-induced platelet aggregation and activation. J Trauma 2004;57:216-23.

20. Zhao WH, Ji XM, Ling F, Ding YC, Xing CH, Wu H, *et al.* Local mild hypothermia induced by intra-arterial cold saline infusion prolongs the time window of onset of reperfusion injury after transient focal ischemia in rats. Neurol Res 2009;31:43-51.

21. Ding Y, Li J, Luan X, Lai Q, McAllister JP 2nd, Phillis 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;54:956-64.

22. 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.

23. Ding Y, Li J, Rafols JA, Phillis JW, Diaz FG. Prereperfusion saline infusion into ischemic territory reduces inflammatory injury after transient middle cerebral artery occlusion in rats. Stroke 2002;33:2492-8.

24. Zhao B, Shang G, Chen J, Geng X, Ye X, Xu G, *et al.* A more consistent intraluminal rhesus monkey model of ischemic stroke. Neural Regen Res 2014;9:2087-94.

25. Wang B, Wu D, Dornbos Iii D, Shi J, Ma Y, Zhang M, *et al.* Local cerebral hypothermia induced by selective infusion of cold lactated ringer's: A feasibility study in rhesus monkeys. Neurol Res 2016;38:545-52.

26. Mattingly TK, Denning LM, Siroen KL, Lehrbass B, Lopez-Ojeda P, Stitt L, *et al.* Catheter based selective hypothermia reduces stroke volume during focal cerebral ischemia in swine. J Neurointerv Surg 2016;8:418-22.

27. 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.

28. Neimark AK, Lee L, Laine A, Pile-Spellman J, Choi J. Brain temperature changes during selective cooling with endovascular intracarotid cold saline infusion: Simulation using human data fitted with an integrated mathematical model. J Neurointerventional Surg 2013;5:165-71.

29. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: The copenhagen stroke study. Stroke 2000;31:2251-6.

30. Ding Y, Justin C. Research progress of hypothermia: Selective

intra-arterial infusion and regional brain cooling in acute stroke therapy. Exp Stroke 2012;11;52-62.
31. Lassen NA. The luxury-perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. Lancet 1966;2:1113-5.
32. Heiss WD, Graf R, Löttgen J, Ohta K, Fujita T, Wagner R, *et al.* Repeat positron emission tomographic studies in transient middle cerebral artery occlusion in cats: Residual perfusion and efficacy of postischemic reperfusion. J Cereb Blood Flow Metab 1997;17:388-400.
33. Pan J, Konstas AA, Bateman B, Ortolano GA, Pile-Spellman J. Reperfusion injury following cerebral ischemia: Pathophysiology, MR imaging, and potential therapies. Neuroradiology 2007;49:93-102.
34. Ding Y, Yao B, Zhou Y, Park H, McAllister JP 2nd, 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. J Neurosurg 2002;96:310-9.
35. Chen J, Fredrickson V, Ding Y, Jiang L, Luo Y, Ji X. The effect of a microcatheter-based selective intra-arterial hypothermia on hemodynamic changes following transient cerebral ischemia. Neurol Res 2015;37:263-8.
36. Luan X, Li J, McAllister JP 2nd, Diaz FG, Clark JC, Fessler RD, *et al.* Regional brain cooling induced by vascular saline infusion into ischemic territory reduces brain inflammation in stroke. Acta Neuropathol 2004;107:227-34.
37. Toyoda T, Suzuki S, Kassell NF, Lee KS. Intraischemic hypothermia attenuates neutrophil infiltration in the rat neocortex after focal ischemia-reperfusion injury. Neurosurgery 1996;39:1200-5.
38. Woitzik J, Schilling L. A new method for superselective middle cerebral artery infusion in the rat. J Neurosurg 2007;106:872-8.
39. Song W, Wu YM, Ji Z, Ji YB, Wang SN, Pan SY. Intra-carotid cold magnesium sulfate infusion induces selective cerebral hypothermia and neuroprotection in rats with transient middle cerebral artery occlusion. Neurol Sci 2013;34:479-86.
40. Chen J, Fredrickson V, Ding Y, Cheng H, Wang N, Ling F, *et al.* Enhanced neuroprotection by local intra-arterial infusion of human albumin solution and local hypothermia. Stroke 2013;44:260-2.
41. Dang S, Liu X, Fu P, Gong W, Yan F, Han P, *et al.* Neuroprotection by local intra-arterial infusion of erythropoietin after focal cerebral ischemia in rats. Neurol Res 2011;33:520-8.
42. van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O›Collins V, *et al.* Can animal models of disease reliably inform human studies? PLoS Med 2010;7:e1000245.
43. Esposito E, Ebner M, Ziemann U, Poli S. In cold blood: Intraarterial cold infusions for selective brain cooling in stroke. J Cereb Blood Flow Metab 2014;34:743-52.
44. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 2012;13:267-78.
45. Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. J Neuroimmunol 2007;184:53-68.
46. Lee JM, Zipfel GJ, Choi DW. The changing landscape of ischaemic brain injury mechanisms. Nature 1999;399:A7-14.
47. Kim JY, Kawabori M, Yenari MA. Innate inflammatory responses in stroke: Mechanisms and potential therapeutic targets. Curr Med Chem 2014;21:2076-97.
48. Hsu CY, Liu TH, Xu J, Hogan EL, Chao J, Sun G, *et al.* Arachidonic acid and its metabolites in cerebral ischemia. Ann N Y Acad Sci 1989;559:282-95.
49. Yenari MA, Han HS. Influence of hypothermia on post-ischemic inflammation: Role of nuclear factor kappa B (NFkappaB). Neurochem Int 2006;49:164-9.
50. Truettner JS, Alonso OF, Dietrich WD. Influence of therapeutic hypothermia on matrix metalloproteinase activity after traumatic brain injury in rats. J Cereb Blood Flow Metab 2005;25:1505-16.
51. Ceulemans AG, Zgavc T, Kooijman R, Hachimi-Idrissi S, Sarre S, Michotte Y. The dual role of the neuroinflammatory response after ischemic stroke: Modulatory effects of hypothermia. J Neuroinflammation 2010;7:74.
52. Nagel S, Su Y, Horstmann S, Heiland S, Gardner H, Koziol J, *et al.* Minocycline and hypothermia for reperfusion injury after focal cerebral ischemia in the rat: Effects on BBB breakdown and MMP expression in the acute and subacute phase. Brain Res 2008;1188:198-206.
53. Zhao H, Li CS, Gong P, Tang ZR, Hua R, Mei X, *et al.* Molecular mechanisms of therapeutic hypothermia on neurological function in a swine model of cardiopulmonary resuscitation. Resuscitation 2012;83:913-20.
54. Kurisu K, Abumiya T, Nakamura H, Shimbo D, Shichinohe H, Nakayama N, *et al.* Transarterial regional brain hypothermia inhibits acute aquaporin-4 surge and sequential microvascular events in ischemia/Reperfusion injury. Neurosurgery 2016;79:125-34.
55. Previch LE, Ma L, Wright JC, Singh S, Geng X, Ding Y. Progress in AQP research and new developments in therapeutic approaches to ischemic and hemorrhagic stroke. Int J Mol Sci 2016;17. pii: E1146.
56. Zhao H, Steinberg GK, Sapolsky RM. General versus specific actions of mild-moderate hypothermia in attenuating cerebral ischemic damage. J Cereb Blood Flow Metab 2007;27:1879-94.
57. Graham SH, Chen J. Programmed cell death in cerebral ischemia. J Cereb Blood Flow Metab 2001;21:99-109.
58. Zhao H, Shimohata T, Wang JQ, Sun G, Schaal DW, Sapolsky RM, *et al.* Akt contributes to neuroprotection by hypothermia against cerebral ischemia in rats. J Neurosci 2005;25:9794-806.
59. Gunn AJ, Gluckman PD. Head cooling for neonatal encephalopathy: The state of the art. Clin Obstet Gynecol 2007;50:636-51.
60. Hoehn T, Hansmann G, Bührer C, Simbruner G, Gunn AJ, Yager J, *et al.* Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. Resuscitation 2008;78:7-12.
61. Shah PS. Hypothermia: A systematic review and meta-analysis of clinical trials. Semin Fetal Neonatal Med 2010;15:238-46.