Review Article

Access this article online
Quick Response Code:

Website: http://www.braincirculation.org
DOI: 10.4103/bc.bc_31_20

# Temporal limits of therapeutic hypothermia onset in clinical trials for acute ischemic stroke: How early is early enough?

**Hangil Lee[1], Yuchuan Ding[1,2]**

**Abstract:**

Stroke is one of the leading causes of mortality and morbidity worldwide, and yet, current treatment is limited to thrombolysis through either t-PA or mechanical thrombectomy. While therapeutic hypothermia has been adopted in clinical contexts such as neuroprotection after cardiac resuscitation and neonatal hypoxic-ischemic encephalitis, it is yet to be used in the context of ischemic stroke. The lack of ameliorative effect in ischemic stroke patients may be tied to the delayed cooling induction onset. In the trials where the cooling was initiated with significant delay (mostly systemic cooling methods), minimal benefit was observed; on the other hand, when cooling was initiated very early (mostly selective cooling methods), there was significant efficacy. Another timing factor that may play a role in amelioration may be the onset of cooling relative to thrombolysis therapy. Current understanding of the pathophysiology of acute ischemic injury and ischemia-reperfusion injury suggests that hypothermia before thrombolysis may be the most beneficial compared to cooling initiation during or after reperfusion. As many of the systemic cooling methods tend to require longer induction periods and extensive, separate procedures from thrombolysis therapy, they are generally delayed to hours after recanalization. On the other hand, selective cooling was generally performed simultaneously to thrombolysis therapy. As we conduct and design therapeutic hypothermia trials for stroke patients, the key to their efficacy may lie in quick and early cooling induction, both respective to the symptom onset and thrombolysis therapy.

**Keywords:**

Acute ischemic stroke, inter-ischemia hypothermia, inter-reperfusion hypothermia, neuroprotection, postreperfusion hypothermia, prereperfusion hypothermia, therapeutic hypothermia

*[1]Department of Neurosurgery, Wayne State University School of Medicine, [2]Department of Research and Development Center, John D. Dingell VA Medical Center, Detroit, Michigan, USA*

**Address for corrspondnece:**
Mr. Hangil Lee, Department of Neurosurgery, Wayne State University School of Medicine, Detroit, Michigan, USA.
E-mail: hangil.lee@med.wayne.edu

Submission: 13-07-2020
Revised: 06-08-2020
Accepted: 24-08-2020
Published: 30-09-2020

## Introduction

Stroke is one of the leading causes of mortality and morbidity worldwide, and yet, current treatment is limited to thrombolysis through either t-PA or mechanical thrombectomy.[1] A promising potential treatment modality identified in animal models is therapeutic hypothermia.[2] Therapeutic hypothermia is currently used in other clinical contexts, such as neuroprotection after cardiac resuscitation[3] and neonatal hypoxic-ischemic encephalitis.[4] Its applications for patients with acute ischemic stroke (AIS) is currently being explored through preclinical and clinical trials.[5]

## Therapeutic Hypothermia Clinical Trials

Clinical trials have verified the plausibility of safely inducing hypothermia in human subjects with AIS.[6-9] The type of hypothermia induced can be divided into two categories: systemic and selective.[10] Systemic hypothermia cools the entire body



**How to cite this article:** Lee H, Ding Y. Temporal limits of therapeutic hypothermia onset in clinical trials for acute ischemic stroke: How early is early enough? Brain Circ 2020;6:139-44.

through surface cooling, endovascular cooling, cold saline infusion, or a combination of the various methods.[6,8] Selective cooling has been most frequently performed by intra-arterial selective cooling infusion (IA-SCI), which induces hypothermia primarily to the brain tissue immediately downstream of the site of mechanical thrombectomy by injecting cold saline.[7]

Most of these trials were Phase I trials, conducted with the intent of determining safety and plausibility. Hence, the sample sizes for these trials were limited. Due to the small samples, the power in assessing therapeutic hypothermia's efficacy on AIS patients is limited. Despite the limited sample size, the benefit of hypothermia seems to diverge contingent on the type of hypothermia, as delineated by Table 1. Of the systemic hypothermia trials listed in the review by Wu *et al*.,[9] 16 authors commented on the efficacy, of which only three trials observed amelioration of some sort, two observed worsened outcomes, and 11 observed inconclusive results; on the other hand, of the selective hypothermia trials in the same review, four commented on their efficacy, of which three observed amelioration of some sort and one observed inconclusive results. While the experiment designs varied widely with the method, onset, duration, and depth of hypothermia, one of the factors was consistently different between the two categories of hypothermia: the starting time of hypothermia.[9]

Therapeutic hypothermia is thought to be ameliorative only if it is performed early enough. Han *et al*. observed that super early, prereperfusion hypothermia was superiorly ameliorative compared to hypothermia induced later.[11] Animal models have also established that early induction is crucial for the ameliorative effects of hypothermia.[12] In agreement with these findings, the current understanding of the pathophysiology of AIS is that many of the pathways to cell damage and eventual death is largely due to ATP depletion,[13] which is ameliorated by slowing down ATP consumption through hypothermia. In other words, hypothermia ameliorates cell damage and death by decreasing the metabolic rate.[13] All of this points to the necessity for early hypothermia induction if we are to hope for ameliorative effects. Any delay in hypothermia is further depletion of ATP and consequently, greater cell death.

**Table 1: Summary of therapeutic hypothermia trials**

| Type of hypothermia | Beneficial outcomes | Worsened outcomes | Total trials |
|---|---|---|---|
| Surface cooling | 3 | 2 | 16 |
| Selective cooling | 3 | - | 4 |

Therapeutic hypothermia trials for acute ischemic stroke patients and their reported efficacy. Those that did not report their outcomes to be either beneficial or worsened found their results to be inconclusive

## Temporal Limitations: Onset Initiation and Induction Length

Regardless of the type of hypothermia, thrombolysis through t-PA or mechanical thrombectomy takes precedence in stroke therapy.[10] Animal models have found that hypothermia, early or delayed, is not beneficial without reperfusion therapy.[2] This prioritization sets a natural parameter for all induction methods of hypothermia. Cooling will be delayed to after reperfusion therapy for the methods that require separate procedures and longer induction times.[14-16] On the other hand, patients can be cooled simultaneous to or before reperfusion, if the procedure can be implemented efficiently and quickly.[7]

## Systemic Hypothermia: Slow Onset Initiation and Long Induction Length

Some common methods of inducing systemic hypothermia are surface cooling, endovascular cooling, cold saline injection, or a combination of the methods. Systemic cooling through any of these methods requires a separate procedure from thrombolysis therapy with long induction times. Depending on the design of the trial, systemic cooling was initiated anytime between 2.05 and 42 h after symptom onset[9] and took 1–7.36 h to reach the target temperature.[17] In these studies, hypothermia had to be induced after thrombolysis therapy to prevent significant delays in reperfusion.

Systemic hypothermia faces additional hurdles that may complicate the cooling process. Cooling the whole body induces a normal physiological response of shivering. This causes the hypothermia induction to be slower as the rapid contraction of the muscles raises the body temperature, which also makes the patient experience uncomfortable.[18] Furthermore, studies have reported a significant incidence of pneumonia of patients that underwent systemic hypothermia, further suggesting its inadequacy in clinical application.[6,15]

## Selective Hypothermia: Quick Onset Initiation and Short Induction Length

IA-SCI is one of the selective cooling methods that have undergone several clinical trials. This cooling method's induction time is restrained to immediately preceding and following reperfusion because it requires vascular access to the internal carotid artery attained during mechanical thrombectomy.[7] In a clinical trial by Wu *et al*., hypothermia was initiated <6 h from symptom onset, concurrent to the thrombolysis procedure through mechanical thrombectomy.[7] While the brain tissue temperature was not directly measured with this trial, it was modeled to effectively cool the ipsilateral

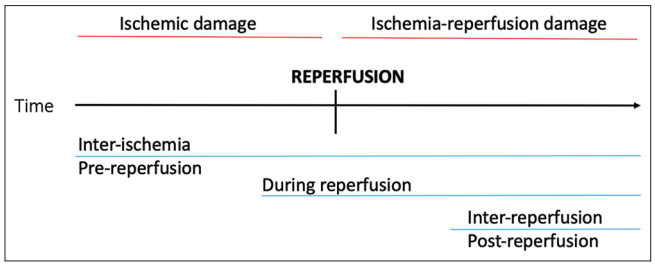


**Figure 1:** The three timings of hypothermia relative to the timing of ischemic damage and ischemia-reperfusion damage

hemisphere to moderate hypothermia (<35°C) within 10 min of injecting cold saline at the rate of >20 ml/min in computer-simulated models.[19] In practice, a slower rate of infusion (10 ml/min) was used preceding thrombectomy to circumvent embolism potential, followed by a higher rate (30 ml/min) immediately following reperfusion.[7]

IA-SCI shows a lot of promise, although it is limited to patients who qualify for mechanical thrombectomy. Unlike systemic cooling, it does not induce shivering,[7] permitting a much more efficient cooling process and comfortable experience for the patient.

## Ideal Hypothermia Induction Timing Parameters

Many studies point to the metabolic nature of acute ischemia's pathophysiology. The damage is thought to occur in two phases: ischemic damage and ischemia-reperfusion damage. Both phases of damage are driven by ATP depletion. In ischemic damage, ATP depletion leads to the failure of various pumps that maintain appropriate ion concentration gradients. Their failure leads to cell swelling, activation of autophagocytic enzymes, and eventual apoptosis activation. For the cells that survive ischemia, ischemia-reperfusion injury poses a continued threat with fresh influx of oxygen and calcium. While oxygen is critical for reactivation of the electron transport chain, it also activates ROS generation in the process through the rapid influx.[13] ROS is further generated through the shunting of xanthine metabolism pathway and nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase, NOX) activation in the absence of ATP.[20] Both ischemic and ischemia-reperfusion injuries can be ameliorated by depressing metabolism. If hypothermia is induced before reperfusion, it will decrease ATP consumption and provide a greater reservoir for crucial ion pump activity, slowing cell death. Furthermore, ischemia-reperfusion injury will also be ameliorated by the provision of additional ATP to prevent further shunting of the xanthine metabolism pathway and slowing down generation of ROS through NOX. If hypothermia is induced after reperfusion, it is unable to diffuse the damage from both mechanisms and can only alleviate the reperfusion damage in the penumbra.

The timing of hypothermia onset has been coined with several different terms. With consideration of the above mechanisms, the onset of hypothermia can be organized into three categories: inter-ischemia/pre-reperfusion (before reperfusion), which is initiated during ischemic damage and before ischemia-reperfusion; during reperfusion, which begins simultaneously to ischemia-reperfusion damage; and inter-reperfusion/post-reperfusion (after reperfusion), which is induced after ischemia-reperfusion damage begins. These terms are visualized by Figure 1. The pathophysiology described above suggests that hypothermia is the most effective if induced inter-ischemia/pre-reperfusion. In support of this, the greatest neuroprotection was observed in cardiac resuscitation patients when they were induced inter-ischemia/prereperfusion.[21]

Using the terminologies described above, the two general categories of hypothermia and their onset timings can be described as follows: systemic hypothermia, due to its cumbersome length of onset and required separate procedure, is induced inter-reperfusion/post-reperfusion; selective hypothermia, as it takes advantage of the intra-arterial access gained in mechanical thrombectomy and quick cooling onset, is induced during reperfusion. These descriptions are organized in Table 2, alongside a preclinical experiment that found ameliorative effects in their therapeutic hypothermia of rats that underwent AIS.

## Additional Discussion on Intra-arterial Selective Cooling Infusion

Selective cooling through IA-SCI is one of the fastest induction methods in clinical trials. It is induced inter-ischemia, and can ameliorate damages caused by both ischemic damage and ischemia-reperfusion damage. Unfortunately, those who can receive IA-SCI are limited to patients who qualify for mechanical thrombectomy, as it requires vascular access to the artery that is supplying the target tissue. Consequently, those who do not qualify for mechanical thrombectomy may not be candidates for IA-SCI. Hence, their cooling methods may be limited to systemic hypothermia. Unfortunately, most of the systemic hypothermia methods that have undergone clinical trials have been delayed to inter-reperfusion hypothermia, induced several hours after thrombolysis treatment. Hypothermia induced inter-reperfusion misses the window of opportunity to ameliorate damages caused by ischemic damage and the beginnings of ischemia-reperfusion damage. In other words, because those who do not qualify for mechanical thrombectomy

**Table 2: Comparison of the parameters of different types of hypothermia**

| | Preclinical experimental findings (rat models) | Systemic hypothermia (surface cooling and endovascular methods) | Selective hypothermia (IA-SCI) |
|---|---|---|---|
| Onset timing | Inter-ischemia/prereperfusion[12] | Inter-reperfusion/postreperfusion (2.05-42 h from symptom onset)[9] | During reperfusion (<6 h from symptom onset)[7] |
| Time to achieve hypothermia | 20 min to reach 35°C[12] | 1-7.36 h to reach 32-35°C[17] | 10 min to reach<35°C with >20 mL/min infusion[19] |

The parameters of different types of hypothermia compared, relative to the findings from preclinical experiments. IA-SCI: Intra-arterial selective cooling infusion

also do not qualify for quick cooling through IA-SCI, they are limited to slower systemic hypothermia, which is unable to ameliorate damages in the crucial time windows.

One potential criticism for IA-SCI is its short duration of cooling and quick rewarming relative to systemic cooling. While some aspects of the pathophysiology of hypothermia's ameliorative effects may indicate that longer duration of cooling is beneficial, meta-analysis of preclinical trials have demonstrated very little, if any, correlation between the duration of cooling and amelioration.[12] Furthermore, the intra-arterial saline flush may benefit the recovery of ischemic tissue with additional mechanisms not achieved by cooling. Inflammatory responses involving increased cytokines and adhesive markers are significant contributors to poor outcomes of ischemic stroke.[22] "Flushing" may further attenuate ischemic injury by reducing the mentioned inflammatory markers in the ischemic area.[23] Some have also raised concerns for increased hemorrhage with IA-SCI. A phase I trial studying the safety of IA-SCI observed no increases in the incidence of intracerebral or symptomatic hemorrhage between the IA-SCI group and control.[7]

## Pharmaceutically Induced Hypothermia: Inter-ischemia/Prereperfusion Hypothermia

One of such promising method for patients who do not qualify for mechanical thrombectomy may be pharmaceutically induced hypothermia. There are eight pharmaceutical classes that are known to induce hypothermia: cannabinoid system, transient receptor potential vanilloid 1-receptor, opioid receptor, neurotensin, thyroxine derivatives, dopamine receptor activators, gaseous hypothermia, and adenosine/adenine nucleotides.[24] The mechanism of cooling is mainly through their effect on the thermoregulation center in the hypothalamus, which also omits shivering in patients observed in systemic cooling methods.[24] Shivering prevention improves the cooling process by preventing counterproductive rewarming and granting the patients a much more comfortable experience.[6] Some of the hypothermic agents, such as some cannabinoids, have also been found to have neuroprotective effects in isolation, independent of cooling.[24] The synergistic potential between hypothermia induction and other neuroprotective effects have great promises in AIS therapy.

Both preclinical and clinical studies that demonstrate pharmaceutically induced hypothermia for AIS are growing in number. A rat model has demonstrated safe and effective pharmaceutically induced inter-ischemia hypothermia through chlorpromazine and promethazine, with neuroprotection demonstrated in both transient and permanent ischemia models.[25] Another pre-clinical study demonstrated that inter-reperfusion pharmaceutical hypothermia through dihydrocapsaicin (DHC) and intra-arterial regional cooling infusions can effectively ameliorate acute ischemic damages.[26]

In clinical trials, effective and efficient neuroprotection in cardiac resuscitation patients was achieved through pharmaceutically induced inter-ischemia hypothermia.[11] As for AIS patient contexts, a clinical trial successfully used caffeinol in conjunction with surface and endovascular cooling to demonstrate safe inter-reperfusion hypothermia in AIS patients.[27]

Other neuroprotective, not necessarily hypothermic, medications may also have synergistic effects with cooling that are yet to be studied. These medications can be organized largely into four categories, based on the deleterious effects they ameliorate: excitotoxicity, reactive oxygen species, cellular apoptosis, and inflammation.[28] Synergistic neuroprotection may be the key to minimizing the drawbacks to pharmaceutically induced hypothermia, which include detrimental side effects, decreased rate of drug metabolism, and challenges to routes of administration. If we discover drug combinations with strong protection and minimized side effects, they may be great candidates for early and quick hypothermia, induced inter-ischemia.

## New Alternative Induction Methods

In their review, Wu *et al*.[9] listed other potential methods of selective hypothermia induction for those who do not qualify for mechanical thrombectomy, which includes epidural cooling,[29] subdural cooling,[30] subarachnoid cooling,[31] and retrograde jugular venous cooling.[32] These require invasive procedures but may become candidates for treating patients who do not qualify for mechanical thrombectomy with improvements to

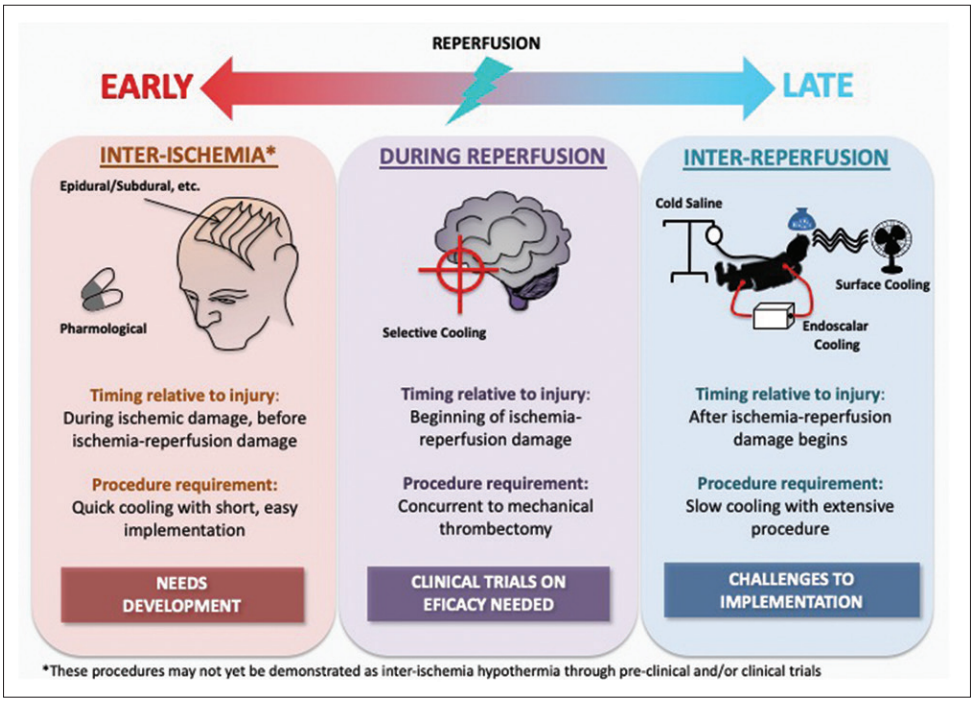


**Figure 2:** Hypothermia induction methods and their respective onset timings relative to reperfusion

make them safer and efficient. Transnasal evaporative cooling is another method that shows promises with limited applications, as its cooling effects are limited to specific areas with limited global cooling in ischemic conditions.[33]

## Conclusion

To reap the fullest or any benefit from therapeutic hypothermia, it is crucial to consider the temporal bounds of hypothermia induction methods. Delayed hypothermia has the potential of providing minimal benefits as it only ameliorates the later stages of ischemia-reperfusion injury. The greatest benefits may be reaped with inter-ischemia hypothermia induction, which may slow the metabolism early enough to ameliorate both ischemic and ischemia-reperfusion injury. IA-SCI may be sufficient for patients who qualify for mechanical thrombectomy with minimal risks and complications due to its smooth integration with mechanical thrombectomy, with cooling induced during reperfusion. Systemic hypothermia through surface, endovascular, and cold saline infusion cooling methods cannot be induced quickly enough and is generally delayed to inter-reperfusion, which is likely too late for both ischemic and ischemia-reperfusion damages. Developing and investing in cooling methods that allow quick inter-ischemia cooling is necessary for patients who do not qualify for mechanical thrombectomy. Of the potential therapies to consider, pharmaceutically induced hypothermia holds great potential for early and quick cooling induction; however, it requires more research to determine safe and effective combinations that have strong cooling effects with wide therapeutic indices.

## Acknowledgment

The authors would like to thank Yoke Ping Khoo Lee for designing Figure 2.

## Financial support and sponsorship

This work was partially supported by Merit Review Award (I01RX-001964-01) from the US Department of Veterans Affairs Rehabilitation R&D Service (Ding).

## Conflicts of interest

There are no conflicts of interest.

## References

1. Minnerup J, Sutherland BA, Buchan AM, Kleinschnitz C. Neuroprotection for stroke: Current status and future perspectives. Int J Mol Sci 2012;13:11753-72.
2. Krieger DW, Yenari MA. Therapeutic hypothermia for acute ischemic stroke: What do laboratory studies teach us? Stroke 2004;35:1482-9.
3. 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.
4. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, *et al*. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med 2012;366:2085-92.
5. Kollmar R, Schwab S. Hypothermia and ischemic stroke. Curr Treat Options Neurol 2012;14:188-96.
6. 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.
7. Wu C, Zhao W, An H, Wu L, Chen J, Hussain M, *et al*. Safety, feasibility, and potential efficacy of intraarterial selective cooling infusion for stroke patients treated with mechanical thrombectomy. J Cereb Blood Flow Metab 2018;38:2251-60.
8. 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.
9. Wu L, Wu D, Yang T, Xu J, Chen J, Wang L, *et al*. Hypothermic neuroprotection against acute ischemic stroke: The 2019 update. J Cereb Blood Flow Metab 2020;40:461-81.
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. Guidelines for the Early Management of Patients with Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke. Vol. 50. Stroke: United States; 2019. p. e344-418.
11. Han Y, Rajah GB, Hussain M, Geng X. Clinical potential of pre-reperfusion hypothermia in ischemic injury. Neurol Res 2019;41:697-703.
12. van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR. Hypothermia in animal models of acute ischaemic stroke: A systematic review and meta-analysis. Brain 2007;130:3063-74.
13. Kurisu K, Yenari MA. Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise. Neuropharmacology 2018;134:302-9.
14. Piironen K, Tiainen M, Mustanoja S, Kaukonen KM, Meretoja A, Tatlisumak T, *et al*. Mild hypothermia after intravenous thrombolysis in patients with acute stroke: A randomized controlled trial. Stroke 2014;45:486-91.
15. Lyden P, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz T, *et al*. Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). Stroke 2016;47:2888-95.
16. 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.
17. Huber C, Huber M, Ding Y. Evidence and opportunities of hypothermia in acute ischemic stroke: Clinical trials of systemic versus selective hypothermia. Brain Circ 2019;5:195-202.
18. Díaz M, Becker DE. Thermoregulation: Physiological and clinical considerations during sedation and general anesthesia. Anesth Prog 2010;57:25-32.
19. Konstas AA, Neimark MA, Laine AF, Pile-Spellman J. A theoretical model of selective cooling using intracarotid cold saline infusion in the human brain. J Appl Physiol (1985) 2007;102:1329-40.
20. Wu MY, Yiang GT, Liao WT, Tsai AP, Cheng YL, Cheng PW, *et al*. Current mechanistic concepts in ischemia and reperfusion injury. Cell Physiol Biochem 2018;46:1650-67.
21. Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, *et al*. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. Circ Cardiovasc Interv 2010;3:400-7.
22. Shen F, Jiang L, Han F, Degos V, Chen S, Su H. Increased inflammatory response in old mice is associated with more severe neuronal injury at the acute stage of ischemic stroke. Aging Dis 2019;10:12-22.
23. Ding Y, Young CN, Li J, Luan X, McAllister JP 2nd, Clark JD, *et al*. Reduced inflammatory mediator expression by pre-reperfusion infusion into ischemic territory in rats: A real-time polymerase chain reaction analysis. Neurosci Lett 2003;353:173-6.
24. Liu K, Khan H, Geng X, Zhang J, Ding Y. Pharmacological hypothermia: A potential for future stroke therapy? Neurol Res 2016;38:478-90.
25. Geng X, Li F, Yip J, Peng C, Elmadhoun O, Shen J, *et al*. Neuroprotection by chlorpromazine and promethazine in severe transient and permanent ischemic stroke. Mol Neurobiol 2017;54:8140-50.
26. Wu D, Zhi X, Duan Y, Zhang M, An H, Wei W, *et al*. Inflammatory cytokines are involved in dihydrocapsaicin (DHC) and regional cooling infusion (RCI)-induced neuroprotection in ischemic rat. Brain Res 2019;1710:173-80.
27. Martin-Schild S, Hallevi H, Shaltoni H, Barreto AD, Gonzales NR, Aronowski J, *et al*. Combined neuroprotective modalities coupled with thrombolysis in acute ischemic stroke: A pilot study of caffeinol and mild hypothermia. J Stroke Cerebrovasc Dis 2009;18:86-96.
28. Link TW, Santillan A, Patsalides A. Intra-arterial neuroprotective therapy as an adjunct to endovascular intervention in acute ischemic stroke: A review of the literature and future directions. Interv Neuroradiol 2020;26:405-15.
29. Zhang L, Cheng H, Shi J, Chen J. Focal epidural cooling reduces the infarction volume of permanent middle cerebral artery occlusion in swine. Surg Neurol 2007;67:117-21.
30. 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.
31. Sourek K, Trávnícek V. General and local hypothermia of the brain in the treatment of intractable epilepsy. J Neurosurg 1970;33:253-9.
32. Duan Y, Wu D, Huber M, Shi J, An H, Wei W, *et al*. New endovascular approach for hypothermia with intrajugular cooling and neuroprotective effect in ischemic stroke. Stroke 2020;51:628-36.
33. 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.