

Oxygen or cooling, to make a decision after acute ischemia stroke

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Abstract

The presence of a salvageable penumbra, a region of ischemic brain tissue with sufficient energy for short-term survival, has been widely agreed as the premise for thrombolytic therapy with tissue plasminogen activator (tPA), which remains the only United States Food and Drug Administration (FDA) approved treatment for acute ischemia stroke. However, the use of tPA has been profoundly constrained due to its narrow therapeutic time window and the increased risk of potentially deadly hemorrhagic transformation (HT). Blood brain barrier (BBB) damage within the thrombolytic time window is an indicator for tPA-induced HT and both normobaric hyperoxia (NBO) and hypothermia have been shown to protect the BBB from ischemia/reperfusion injury. Therefore, providing the O₂ as soon as possible (NBO treatment), freezing the brain (hypothermia treatment) to slow down ischemia-induced BBB damage or their combined use may extend the time window for the treatment of tPA. In this review, we summarize the protective effects of NBO, hypothermia or their use combined with tPA on ischemia stroke, based on which, the combination of NBO and hypothermia may be an ideal early stroke treatment to preserve the ischemic penumbra. Given this, there is an urge for large randomized controlled trials to address the effect.

Key words: normobaric hyperoxia; hypothermia; ischemic stroke; tissue plasminogen activator; neuroprotection; blood brain barrier; thrombolysis; hemorrhage transformation

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INTRODUCTION

Acute ischemic stroke (AIS) is the most common form of stroke and an almost immediate loss of oxygen and glucose to the brain tissue occurred when blood vessel is suddenly occluded by a thrombus or embolism (Lakhan et al., 2013). Ischemic penumbra is a region of ischemic brain tissue with sufficient energy for short-term survival (Hakim, 1998) and if ischemia duration is extended, the penumbra will progress to irreversible damage (Dirnagl et al., 1999). Therefore, the primary goal of current treatment for AIS is to salvage the

penumbra (Ramos-Cabrer et al., 2011), which has inspired the development of two main categories of drugs to treat AIS: some drugs to interrupt cell death pathways (Reza Noorian et al., 2011) and other drugs to induce reperfusion (Barreto and Alexandrov, 2012). Over decades, research has failed to translate over 1,000 experimental treatments from discovery in cells and rodents to use in humans (O'Collins et al., 2012) and a major goal in the treatment of AIS is to prompt arterial recanalization. Until now, thrombolysis with tissue plasminogen activator (tPA) within 3 or 4.5 hours



after symptom onset is the only approved treatment by the United States Food and Drug Administration (FDA) for AIS (Hacke et al., 2008; Del Zoppo et al., 2009; Peplow, 2015). However, brief therapeutic window and the high incidence of hemorrhage transformation (HT) have profoundly constrained the clinical use of tPA in ischemic stroke patients (Marshall, 2015).

The presence of a salvageable penumbra has been widely agreed as the premise for thrombolytic therapy (Ramos-Cabrer et al., 2011), while protecting the blood brain barrier (BBB) is critical to avoid brain edema and HT following reperfusion therapy. In the early stage of AIS, ischemia-induced hypoxia and the consequent bioenergetic failure produced irreversible damage to the penumbra, and BBB damage within the thrombolytic time window is an indicator for tPA-induced HT (Jin et al., 2014; Leigh et al., 2014). Therefore, either providing the O₂ as soon as possible (normobaric hyperoxia (NBO) treatment), freezing the brain (hypothermia) to slow down the ischemia-induced damage or both treatments will extend the time window of tPA treatment.

EFFECT OF NBO TREATMENT

NBO's protective effect

Improving tissue oxygenation has been studied for many years as a simplistic but plausible treatment strategy to reduce ischemia-induced injury. Recent animal and human stroke studies showed that when administered early after ischemia onset, NBO showed neuroprotective effects (Qi et al., 2013). For example, NBO retards the evolution of ischemic brain tissue toward infarction in a rat model of transient focal cerebral ischemia (Xu et al., 2016). This protection is attributed to NBO's ability to improve energy metabolism in the ischemic penumbra, as evidenced by elevated interstitial oxygen partial pressure (Liu et al., 2006), increased cerebral blood flow and O₂ delivery (Chazalviel et al., 2016c), reductions in acidosis and adenosine triphosphate (ATP) deletion (Sun et al., 2011), and reduced caspase-3 and -9 expression (Chen et al., 2015). Of note, continued NBO treatment after reperfusion shows more beneficial effects than NBO treatment during occlusion alone (Tiwari et al., 2016).

Side effect and controversy of NBO

As NBO is readily available, safe and can be initiated promptly after stroke onset by paramedics, it has been suggested as a practical acute-phase treatment to slow down the onset of irreversible damage of the penumbra, thus potentially allowed for delayed or more effective thrombolysis (Kim et al., 2005; Henninger and Fisher, 2006; Liu et al., 2009). In addition, NBO has been shown

as an effective neuroprotective strategy for ischemic stroke (Cornet et al., 2012; Qi et al., 2013; Shi et al., 2016). However, recent clinical trial was terminated because of unclear therapeutic efficacy (95 % NBO in AIS) (Cornet et al., 2012; Pountain and Roffe, 2012). In addition, in a recent Indian trial using 61 % NBO for anterior circulation ischemic strokes patients within 12 hours after stroke, NBO did not significantly improve their clinical outcome (Padma et al., 2011). This is maybe due to the complexity of stroke and detrimental potential of oxygen-associated excessive generation of reactive oxygen series (ROS). However, a recent critical review of the literature showed that NBO does not increase ROS or oxidative stress if applied for a short duration; therefore, the potential that NBO is a viable neuroprotective strategy for AIS is compelling. The benefits of NBO may significantly outweigh the risks of potential increase in ROS generation for the treatment of AIS (Weaver and Liu, 2015).

Combination treatment with NBO

Since NBO alone did not work as expected, combination NBO with other therapy may be an ideal strategy (Liang et al., 2016). For example, recent studies showed that NBO extended neuro- and vaso-protection of N-acetylcysteine in transient focal ischemia (Liu et al., 2016), combination of NBO and melatonin demonstrated more protective effect on reperfusion injury through regulation cerebral micro-circulation (Beker et al., 2015). In addition, combination therapy of NBO with methylene blue improved functional outcome and reduced infarct volume compared to either treatment alone and these improvements extended up to 28 days (Rodriguez et al., 2016).

Effect of hyperbaric oxygen (HBO) treatment

HBO is an efficacious, benign and humanitarian way to promote brain repair (Stoller, 2015). It has showed protective effect on traumatic brain injury (Hu et al., 2016). Of note, HBO increased tPA-induced thrombolysis *in vitro*, and reduced ischemic brain damage and edema in rats subjected to thromboembolic brain ischemia (Chazalviel et al., 2016b). In addition, HBO, but not NBO, reduced oxygen and glucose deprivation-induced cell injury (Chazalviel et al., 2016a). More interestingly, numerous basic and clinical studies have shown the beneficial effect of HBO on neurological outcome after stroke; however, HBO's effect in human stroke is still not sufficiently evidence-based, due to the insufficient randomized double-blind controlled clinical studies (Zhai et al., 2016).

Effect of NBO treatment with tPA thrombolysis

NBO could increase the safety of delayed tPA thrombolysis



in stroke (Liu et al., 2009) and has been shown to slow BBB damage and expand the therapeutic time window for tPA treatment in cerebral ischemia (Liang et al., 2015). More importantly, it did not increase cellular markers of superoxide generation or brain levels of matrix metalloprotein-9 (MMP-9) (Kim et al., 2005). Despite producing cerebral blood flow restoration, combination of NBO with tPA had no neuroprotective effect on ischemic brain damage (David et al., 1985); however, Henninger et al. (2009) showed that the combination of NBO with tPA did not increase hemorrhage volume at 10 hours or petechial hemorrhages at 24 hours in a clinically relevant thromboembolic rat stroke model.

EFFECT OF HYPOTHERMIA TREATMENT

Hypothermia's protective effect

Hypothermia has been suggested to be the most potent therapeutic approach to reduce experimental ischemic brain injury, and mild hypothermia (MH) is increasingly used for neuroprotection during neurovascular surgery. Mild to moderate hypothermia prevented microvascular basal lamina antigen loss in experimental focal cerebral ischemia (Hamann et al., 2004) and tPA-related hemorrhage after experimental stroke (Tang et al., 2013), reduced infarct volume and BBB breakdown following tPA treatment in the mouse (Cechmanek et al., 2015), diminished oxidative DNA damage and pro-death signaling events after cerebral ischemia (Ji et al., 2007). Hypothermia also established a lasting inhibitory effect on activation of astrogliosis (Zgavc et al., 2012).

Since cooling therapy may reduce damage and potentially improve outcome, MH is a promising neuroprotective therapy in stroke management. In addition, head cooling targets the site of injury and may have fewer side effects than systemic cooling (Kollmar and Schwab, 2012).

Controversy of delayed hypothermia treatment

Perhaps the best studied neuroprotective treatment in ischemia models is MH. Extensive data showed that hypothermia lead to decreased infarct volumes and improved outcomes in ischemic animal models (Choi et al., 2012). Despite these findings, MH application in ischemic stroke has been limited by delayed cooling onset, prolonged duration, extensive medical and nursing efforts, and significant complications (Han et al., 2015).

Although a large pool of evidence has demonstrated that MH is beneficial if it is given during cerebral ischemia, there are also controversial reports. For example, in embolic model, inflammatory reactions occurring in the brain after ischemia may contribute to secondary damage (Wang et al., 2002). Delayed administration of minocycline alone or

delayed minocycline plus delayed MH reduced the infarction volume significantly (Wang et al., 2003). However, delayed MH alone was not protective and delayed MH in combination with minocycline did not show any additive effects (Wang et al., 2002; Wang et al., 2003).

Combination treatment with hypothermia

The proposed combination therapy, which is based on pathophysiological considerations, seems to be a promising alternative for neuroprotection in cerebrovascular surgery (Zausinger et al., 2003). Combination of therapeutic hypothermia and other neuroprotective strategies after ischemic cerebral insult has been reviewed (Goossens and Hachimi-Idrissi, 2014). Combined MH and decompressive craniectomy (DC) result in additional reduction of infarction size and improve neurological score (Doerfler et al., 2001). In addition, MH plus DC not only ameliorates neuron apoptosis but also remarkably reduces infarction size (Jieyong et al., 2006). Shuaib et al. (1993) showed that when CGS-19755, an N-methyl-D-aspartic acid (NMDA) receptor blocker, was combined with MH, the effects of repetitive ischemia were completely abolished in all but one gerbil. Combination of hypothermia with MH may further enhance this protection. Nito et al. (2004) showed that combination of MH with FK506, an immunosuppressant, significantly reduced ischemic brain damage following transient middle cerebral artery occlusion in rats, and expanded the therapeutic window of FK506. Sahin et al. (2010) demonstrated that the combination of citicoline with MH was more effective than either alone in ameliorating cerebral damage after transient focal ischemia by suppressing apoptotic processes. Berger et al. (2004) provided evidence that combining MH and brain-derived neurotrophic factor (BDNF) in the acute stage of ischemia had a synergistic effect in attenuating striatal glutamate release and reducing early infarct size.

Mild hypothermia with tPA thrombolysis

Hypothermia is neuroprotective in experimental stroke and may extend the so far limited therapeutic time window for thrombolysis. MH reduced tPA-related hemorrhage and BBB disruption after experimental stroke (Tang et al., 2013). When MH and thrombolysis was combined in experimental thromboembolic stroke, there was no significant difference between the use of t-PA alone or in combination with hypothermia (Kollmar et al., 2004).

COMBINATION OF OXYGEN WITH COOLING

Issues must be addressed before hypothermia treatment is implemented at a clinical level (Han et al., 2015). Combination therapy of NBO with MH prevented brain damage from thromboembolic stroke via protein kinase C-protein kinase B-nitric oxide metabolite (PKC-AKT-NOX) modulation,



reduced hyperglycolysis and modulated pyruvate dehydrogenase complex in thromboembolic cerebral ischemia (Cai et al., 2016a, b, c). Of note, therapeutic effect of tPA in ischemic stroke was enhanced in combination with NBO and hypothermia (Ji et al., 2015); therefore, it is reasonable to combine NBO and MH after acute ischemia stroke.

CONCLUSION

As NBO and MH are widely available and can be promptly initiated after stroke onset, combination of NBO and MH may be an ideal early stroke treatment to preserve the ischemic penumbra, followed by other neuroprotectants to eventually salvage the ischemic penumbral tissue. Because of the high translational degree of both NBO and MH (they are cost-effective, easy to manage, simple to administer, and readily available), there is an urge for large randomized controlled trials to address the effect.

Author contributions

WCL reviewed the studies, wrote up the manuscript. X CJ participated in the overall design of the review and obtained partial funding. All authors have read and approved the final version of this paper.

Conflicts of interest

The authors declare no competing financial interests

Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

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REFERENCES

- Barreto AD, Alexandrov AV (2012) Adjunctive and alternative approaches to current reperfusion therapy. *Stroke* 43:591-598.
- Beker MC, Caglayan AB, Kelestemur T, Caglayan B, Yalcin E, Yulug B, Kilic U, Hermann DM, Kilic E (2015) Effects of normobaric oxygen and melatonin on reperfusion injury: role of cerebral microcirculation. *Oncotarget* 6:30604-30614.
- Berger C, Schabitz WR, Wolf M, Mueller H, Sommer C, Schwab S (2004) Hypothermia and brain-derived neurotrophic factor reduce glutamate synergistically in acute stroke. *Exp Neurol* 185:305-312.
- Cai L, Thibodeau A, Peng C, Ji X, Rastogi R, Xin R, Singh S, Geng X, Rafols JA, Ding Y (2016a) Combination therapy of normobaric oxygen with hypothermia or ethanol modulates pyruvate dehydrogenase complex in thromboembolic cerebral ischemia. *J Neurosci Res* 94:749-758.
- Cai L, Stevenson J, Geng X, Peng C, Ji X, Xin R, Rastogi R, Sy C, Rafols JA, Ding Y (2016b) Combining normobaric oxygen with ethanol or hypothermia prevents brain damage from thromboembolic stroke via PKC-Akt-NOX modulation. *Mol Neurobiol* doi: 10.1007/s12035-016-9695-7.
- Cai L, Stevenson J, Peng C, Xin R, Rastogi R, Liu K, Geng X, Gao Z, Ji X, Rafols JA, Ji Z, Ding Y (2016c) Adjuvant therapies using normobaric oxygen with hypothermia or ethanol for reducing hyperglycolysis in thromboembolic cerebral ischemia. *Neuroscience* 318:45-57.
- Cechmanek BK, Tuor UI, Rushforth D, Barber PA (2015) Very mild hypothermia (35 degrees c) postischemia reduces infarct volume and blood/brain barrier breakdown following tpa treatment in the mouse. *Ther Hypothermia Temp Manag* 5:203-208.
- Chazalviel L, Blatteau JE, Vallee N, Risso JJ, Besnard S, Abraini JH (2016a) Effects of normobaric versus hyperbaric oxygen on cell injury induced by oxygen and glucose deprivation in acute brain slices. *Med Gas Res* 6:169-173.
- Chazalviel L, Haelewyn B, Degoulet M, Blatteau JE, Vallee N, Risso JJ, Besnard S, Abraini JH (2016b) Hyperbaric oxygen increases tissue-plasminogen activator-induced thrombolysis in vitro, and reduces ischemic brain damage and edema in rats subjected to thromboembolic brain ischemia. *Med Gas Res* 6:64-69.
- Chazalviel L, David HN, Haelewyn B, Blatteau JE, Vallee N, Risso JJ, Besnard S, Abraini JH (2016c) The underestimated effect of normobaric hyperoxia on cerebral blood flow and its relationship to neuroprotection. *Brain* doi:10.1093/brain/aww178.
- Chen S, Peng H, Rowat A, Gao F, Zhang Z, Wang P, Zhang W, Wang X, Qu L (2015) The effect of concentration and duration of normobaric oxygen in reducing caspase-3 and -9 expression in a rat-model of focal cerebral ischaemia. *Brain Res* 1618:205-211.
- Choi KE, Hall CL, Sun JM, Wei L, Mohamad O, Dix TA, Yu SP (2012) A novel stroke therapy of pharmacologically induced hypothermia after focal cerebral ischemia in mice. *FASEB J* 26:2799-2810.
- Cornet AD, Kooter AJ, Peters MJ, Smulders YM (2012) Supplemental oxygen therapy in medical emergencies: more harm than benefit? *Arch Intern Med* 172:289-290.
- David HN, Haelewyn B, Degoulet M, Colomb DG Jr, Risso JJ, Abraini JH (1985) Prothrombolytic action of normobaric oxygen given alone or in combination with recombinant tissue-plasminogen activator in a rat model of thromboembolic stroke. *J Appl Physiol* (1985) 112:2068-2076.
- Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr (2009) Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke* 40:2945-2948.
- Dirnagl U, Iadecola C, Moskowitz MA (1999) Pathobiology of ischemic stroke: an integrated view. *Trends Neurosci* 22:391-397.
- Doerfler A, Schwab S, Hoffmann TT, Engelhorn T, Forsting M (2001) Combination of decompressive craniectomy and mild hypothermia ameliorates infarction volume after permanent focal ischemia in rats. *Stroke* 32:2675-2681.
- Goossens J, Hachimi-Idrissi S (2014) Combination of therapeutic hypothermia and other neuroprotective strategies after an ischemic cerebral insult. *Curr Neuropharmacol* 12:399-412.
- Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 359:1317-1329.



- Hakim AM (1998) Ischemic penumbra: the therapeutic window. *Neurology* 51:S44-46.
- Hamann GF, Burggraf D, Martens HK, Liebetrau M, Jager G, Wunderlich N, DeGeorgia M, Krieger DW (2004) Mild to moderate hypothermia prevents microvascular basal lamina antigen loss in experimental focal cerebral ischemia. *Stroke* 35:764-769.
- Han Z, Liu X, Luo Y, Ji X (2015) Therapeutic hypothermia for stroke: Where to go? *Exp Neurol* 272:67-77.
- Henninger N, Fisher M (2006) Normobaric hyperoxia—a promising approach to expand the time window for acute stroke treatment. *Cerebrovasc Dis* 21:134-136.
- Henninger N, Bratane BT, Bastan B, Bouley J, Fisher M (2009) Normobaric hyperoxia and delayed tPA treatment in a rat embolic stroke model. *J Cereb Blood Flow Metab* 29:119-129.
- Hu Q, Manaenko A, Xu T, Guo Z, Tang J, Zhang JH (2016) Hyperbaric oxygen therapy for traumatic brain injury: bench-to-bedside. *Med Gas Res* 6:102-110.
- Ji X, Luo Y, Ling F, Stetler RA, Lan J, Cao G, Chen J (2007) Mild hypothermia diminishes oxidative DNA damage and pro-death signaling events after cerebral ischemia: a mechanism for neuroprotection. *Front Biosci* 12:1737-1747.
- Ji Z, Liu K, Cai L, Peng C, Xin R, Gao Z, Zhao E, Rastogi R, Han W, Rafols JA, Geng X, Ding Y (2015) Therapeutic effect of tPA in ischemic stroke is enhanced by its combination with normobaric oxygen and hypothermia or ethanol. *Brain Res* 1627:31-40.
- Jieyong B, Zhong W, Shiming Z, Dai Z, Kato Y, Kanno T, Sano H (2006) Decompressive craniectomy and mild hypothermia reduces infarction size and counterregulates Bax and Bcl-2 expression after permanent focal ischemia in rats. *Neurosurg Rev* 29:168-172.
- Jin X, Liu J, Liu W (2014) Early ischemic blood brain barrier damage: a potential indicator for hemorrhagic transformation following tissue plasminogen activator (tPA) thrombolysis? *Curr Neurovasc Res* 11:254-262.
- Kim HY, Singhal AB, Lo EH (2005) Normobaric hyperoxia extends the reperfusion window in focal cerebral ischemia. *Ann Neurol* 57:571-575.
- Kollmar R, Schwab S (2012) Hypothermia and Ischemic Stroke. *Curr Treat Options Neurol* doi:10.1007/s11940-012-0164-y.
- Kollmar R, Henninger N, Bardutzky J, Schellinger PD, Schabitz WR, Schwab S (2004) Combination therapy of moderate hypothermia and thrombolysis in experimental thromboembolic stroke—an MRI study. *Exp Neurol* 190:204-212.
- Lakhan SE, Kirchgessner A, Tepper D, Leonard A (2013) Matrix metalloproteinases and blood-brain barrier disruption in acute ischemic stroke. *Front Neurol* 4:32.
- Leigh R, Jen SS, Hillis AE, Krakauer JW, Barker PB (2014) Pre-treatment blood-brain barrier damage and post-treatment intracranial hemorrhage in patients receiving intravenous tissue-type plasminogen activator. *Stroke* 45:2030-2035.
- Liang J, Qi Z, Liu W, Wang P, Shi W, Dong W, Ji X, Luo Y, Liu KJ (2015) Normobaric hyperoxia slows blood-brain barrier damage and expands the therapeutic time window for tissue-type plasminogen activator treatment in cerebral ischemia. *Stroke* 46:1344-1351.
- Liang LJ, Yang JM, Jin XC (2016) Cocktail treatment, a promising strategy to treat acute cerebral ischemic stroke? *Med Gas Res* 6:33-38.
- Liu S, Liu W, Ding W, Miyake M, Rosenberg GA, Liu KJ (2006) Electron paramagnetic resonance-guided normobaric hyperoxia treatment protects the brain by maintaining penumbral oxygenation in a rat model of transient focal cerebral ischemia. *J Cereb Blood Flow Metab* 26:1274-1284.
- Liu W, Hendren J, Qin XJ, Liu KJ (2009) Normobaric hyperoxia reduces the neurovascular complications associated with delayed tissue plasminogen activator treatment in a rat model of focal cerebral ischemia. *Stroke* 40:2526-2531.
- Liu Y, Liu WC, Sun Y, Shen X, Wang X, Shu H, Pan R, Liu CF, Liu W, Liu KJ, Jin X (2016) Normobaric hyperoxia extends neuro- and vaso-protection of N-acetylcysteine in transient focal ischemia. *Mol Neurobiol* doi:10.1007/s2035-016-9932-0.
- Marshall RS (2015) Progress in intravenous thrombolytic therapy for acute stroke. *JAMA Neurol* 72:928-934.
- Nito C, Kamiya T, Ueda M, Arai T, Katayama Y (2004) Mild hypothermia enhances the neuroprotective effects of FK506 and expands its therapeutic window following transient focal ischemia in rats. *Brain Res* 1008:179-185.
- O'Collins VE, Macleod MR, Donnan GA, Howells DW (2012) Evaluation of combination therapy in animal models of cerebral ischemia. *J Cereb Blood Flow Metab* 32:585-597.
- Padma MV, Bhasin A, Bhatia R, Garg A, Singh MB, Tripathi M, Prasad K (2011) Normobaric oxygen therapy in acute ischemic stroke: A pilot study in Indian patients. *Ann Indian Acad Neurol* 13:284-288.
- Peplow PV (2015) Neuroimmunomodulatory effects of transcranial laser therapy combined with intravenous tPA administration for acute cerebral ischemic injury. *Neural Regen Res* 10:1186-1190.
- Pountain SJ, Roffe C (2012) Does routine oxygen supplementation in patients with acute stroke improve outcome? *BMJ* 345:e6976.
- Qi Z, Liu W, Luo Y, Ji X, Liu KJ (2013) Normobaric hyperoxia-based neuroprotective therapies in ischemic stroke. *Med Gas Res* 3:2.
- Ramos-Cabrer P, Campos F, Sobrino T, Castillo J (2011) Targeting the ischemic penumbra. *Stroke* 42:S7-11.
- Reza Noorian A, Nogueira R, Gupta R (2011) Neuroprotection in acute ischemic stroke. *J Neurosurg Sci* 55:127-138.
- Rodriguez P, Zhao J, Milman B, Tiwari YV, Duong TQ (2016) Methylene blue and normobaric hyperoxia combination therapy in experimental ischemic stroke. *Brain Behav* 6:e00478.
- Sahin S, Alkan T, Temel SG, Tureyen K, Tolunay S, Korfali E (2010) Effects of citicoline used alone and in combination with mild hypothermia on apoptosis induced by focal cerebral ischemia in rats. *J Clin Neurosci* 17:227-231.
- Shi SH, Qi ZF, Luo YM, Ji XM, Liu KJ (2016) Normobaric oxygen treatment in acute ischemic stroke: a clinical perspective. *Med Gas Res* 6:147-153.
- Shuaib A, Ijaz S, Mazagri R, Senthilsevlvan A (1993) CGS-19755 is neuroprotective during repetitive ischemia: this effect is significantly enhanced when combined with hypothermia. *Neuroscience* 56:915-920.
- Stoller KP (2015) All the right moves: the need for the timely use of hyperbaric oxygen therapy for treating TBI/CTE/PTSD. *Med Gas Res* 5:7-12.
- Sun L, Strelow H, Mies G, Veltkamp R (2011) Oxygen therapy improves energy metabolism in focal cerebral ischemia. *Brain Res* 1415:103-108.



- Tang XN, Liu L, Koike MA, Yenari MA (2013) Mild hypothermia reduces tissue plasminogen activator-related hemorrhage and blood brain barrier disruption after experimental stroke. *Ther Hypothermia Temp Manag* 3:74-83.
- Tiwari YV, Jiang Z, Sun Y, Du F, Rodriguez P, Shen Q, Duong TQ (2016) Effects of stroke severity and treatment duration in normobaric hyperoxia treatment of ischemic stroke. *Brain Res* 1635:121-129.
- Wang CX, Yang T, Shuaib A (2003) Effects of minocycline alone and in combination with mild hypothermia in embolic stroke. *Brain Res* 963:327-329.
- Wang CX, Yang T, Noor R, Shuaib A (2002) Delayed minocycline but not delayed mild hypothermia protects against embolic stroke. *BMC Neurol* 2:2.
- Weaver J, Liu KJ (2015) Does normobaric hyperoxia increase oxidative stress in acute ischemic stroke? A critical review of the literature. *Med Gas Res* 5:11.
- Xu J, Zhang Y, Liang Z, Wang T, Li W, Ren L, Huang S, Liu W (2016) Normobaric hyperoxia retards the evolution of ischemic brain tissue toward infarction in a rat model of transient focal cerebral ischemia. *Neurol Res* 38:75-79.
- Zausinger S, Westermaier T, Plesnila N, Steiger HJ, Schmid-Elsaesser R (2003) Neuroprotection in transient focal cerebral ischemia by combination drug therapy and mild hypothermia: comparison with customary therapeutic regimen. *Stroke* 34:1526-1532.
- Zgave T, Ceulemans AG, Hachimi-Idrissi S, Kooijman R, Sarre S, Michotte Y (2012) The neuroprotective effect of post ischemic brief mild hypothermic treatment correlates with apoptosis, but not with gliosis in endothelin-1 treated rats. *BMC Neurosci* 13:105.
- Zhai WW, Sun L, Yu ZQ, Chen G (2016) Hyperbaric oxygen therapy in experimental and clinical stroke. *Med Gas Res* 6:111-118.