Sevoflurane: an opportunity for stroke treatment

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Abstract

In developed countries, stroke is the leading cause of death and disability that affects long-term quality of life and its incidence is increasing. The incidence of ischemic stroke is much higher than that of hemorrhagic stroke. Ischemic stroke often leads to very serious neurological sequelae, which severely reduces the patients' quality of life and becomes a social burden. Therefore, ischemic stroke has received increasing attention. As a new type of anesthetic, sevoflurane has a lower solubility, works faster in the human body, and has less impact on the cardiovascular system than isoflurane. At the same time, studies have shown that preconditioning and postconditioning with sevoflurane have a beneficial effect on stroke. We believe that the role of sevoflurane in stroke may be a key area for future research. Therefore, this review mainly summarizes the relevant mechanisms of sevoflurane preconditioning and postconditioning in stroke in the past 20 years, revealing the bright prospects of sevoflurane in stroke treatment.

Key words: apoptosis; calcium overload; cerebral ischemia/reperfusion injury; excitotoxicity; inflammatory response; sevoflurane preconditioning and postconditioning; sevoflurane; stroke

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Introduction

At present, stroke is a leading cause of abnormal death and long-term disability in developed countries, and the incidence of stroke is still on the rise. Stroke is a human cerebrovascular disease, including arterial stenosis, occlusion or rupture caused by various known or unknown reasons, which eventually leads to a cerebral blood circulation disorder, often an acute attack.[1] Stroke can be divided into acute ischemic stroke and acute hemorrhagic stroke according to the type of attack.[1] Ischemic stroke can be divided into arteriosclerotic thrombotic cerebral infarction, cardiogenic cerebral embolism and lacunar cerebral infarction.[1] Hemorrhagic stroke can be divided into cerebral hemorrhage, subarachnoid hemorrhage, and intracranial vascular rupture caused by hypertension or other causes (**Figure 1**).[1]

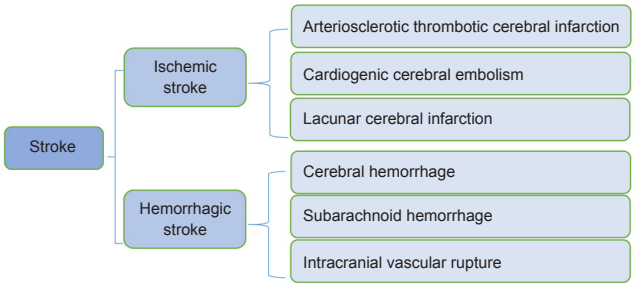

Figure 1: Different types of stroke and their classification.

The incidence of ischemic stroke is much higher than that of hemorrhagic stroke.[1] Ischemic stroke is the third leading cause of death worldwide.[2] It causes disability in up to 0.2% of the world's population every year.[3] The burden of stroke-related disabilities is also high and has an increasing globle trend. This is mainly due to the aging of the population in high-income countries and the accumulation of stroke risk factors in low- and middle-income countries, such as smoking, hypertension and obesity.[4] Ischemic stroke can lead to very serious neurological sequelae, seriously reduce the prognosis of patients' quality of life, and become a social burden. Therefore, researchers are paying increasing attention to the study of ischemic stroke.

Currently, the preferred treatment options for ischemic stroke are vascular recanalization and the use of anticoagulants. However, because of its narrow time window of treatment,[5] this method is relatively limited in clinical application and can only be performed after the occurrence of cerebral ischemic events. Wells et al.[6] found that patients under general anesthesia have a higher tolerance to cerebral ischemia than normal people. In fact, all kinds of brain injury often share similar potential pathophysiological mechanisms. Based on this foundation, it has inspired subsequent research on the related brain-protective effects of various medical gases in brain injury, including stroke, ischemia/hemorrhage, traumatic brain injury, subarachnoid hemorrhage, and other nerve injury models. It covers some volatile gases, such as isoflurane, sevoflurane, halothane, enflurane and desflurane,[7-11] non-volatile gases, such as xenon and nitrous oxide, common gases, such as oxygen,[12] inert gases,[13] and other toxic gases, such as hydrogen sulfide[14] and carbon monoxide, have also been proven to have neuroprotective effects.[15] Among these neuroprotective gases, oxygen and anesthetics (isoflurane and sevoflurane) are of the most concern, possibly because they have already been used in clinical practice. For example, hyperbaric oxygen is widely used for rehabilitation treatment of certain respiratory diseases and cerebral infarction, and has significant positive effects.

Also as an anesthetic, isoflurane, as a new type of anesthetic, has lower solubility compared with sevoflurane, and the speed of induction, anesthesia or awakening is faster, indicating that the faster it acts in the human body, which is more suitable for stroke, an acute onset brain injury. At the same time, sevoflurane has less impact on the cardiovascular system than isoflurane, and the elderly are the main people who are prone to stroke. In general, the elderly are also more likely to have poor cardiovascular function, making sevoflurane more suitable for use in stroke events than isoflurane. In addition, they are safe, fat soluble, and highly permeable to the blood-brain barrier, which is crucial for delivery to the brain.[16] However, through the retrieval of relevant literature, we found that there are a certain number of relevant studies on isoflurane in stroke, while the research on sevoflurane in stroke is not very sufficient. Therefore, this paper focuses on exploring the role of sevoflurane in stroke events. Given that ischemic stroke is the most important type of stroke, we mainly explore the role of sevoflurane in ischemic stroke.

Cerebral ischemia/reperfusion injury is a major cause of poor prognosis in most patients with ischemic stroke. The mechanism of cerebral ischemic injury is very complex. Existing relevant studies indicate that its brain injury mechanism may involve oxidative stress,[17-20] calcium overload,[21,22] excitotoxicity,[23-25] inflammatory reaction,[26-30] apoptosis,[31-33] blood brain barrier damage, and other mechanisms.

Oxidative Stress

The human brain is rich in lipids and is easily affected by oxidative stress. Therefore, antioxidant methods play an important role in protecting the brain from various injuries caused by ischemia.[34,35] Oxidative stress is one of the main mechanisms underlying the occurrence and development of human cerebral ischemia/reperfusion injury.[36,37] The intense oxidative stress after stroke is an important reason for the occurrence and development of severe nerve injury. Under normal circumstances, there is a dynamic balance between intracellular oxidative stress and endogenous antioxidant systems. However, in the case of ischemia/reperfusion, the production of reactive oxygen species will increase dramatically, exceeding the endogenous antioxidant system, leading to oxidative stress. In this case, excessive oxidative stress can lead to an imbalance that ultimately leads to neuronal damage.[38] Normal organisms have a built-in antioxidant system, and nuclear factor erythroid 2-related factor 2 (Nrf2) is a key member of this system. Nrf2 is an important transcription factor that controls the expression of a series of antioxidant enzymes.[39,40] Under physiological conditions, Nrf2 is isolated in the cytoplasm of cells and rapidly degraded by S26 proteasome after synthesis.[16] The downstream genes of Nrf2 include four groups of antioxidant enzymes[38,39]: detoxification enzyme, glutathione group, thioredoxin group and transferase group. Sevoflurane, as one of the Nrf2 activators, can alleviate cerebral ischemia/reperfusion injury by regulating the activity of brain antioxidant enzymes and inhibiting oxidative stress after treatment.[40,41] Malondialdehyde is one of the end products of lipid peroxidation. Thus, the level of malondialdehyde indirectly reflects the level of oxygen free radicals and the degree of lipid peroxidation in brain tissue, while sevoflurane post-treatment can significantly reduce blood lipid and malondialdehyde levels and increase normal pyramidal neuron density in rats with cerebral ischemia/reperfusion (**Figure 2**).[42-44]

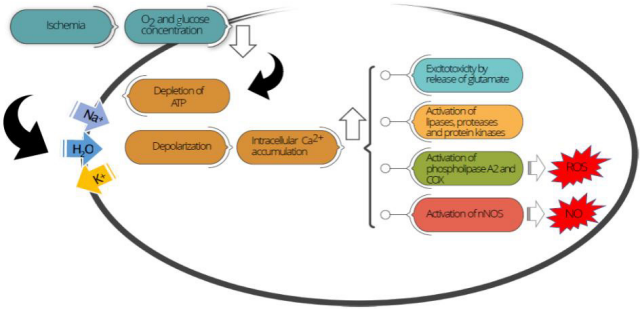

Figure 2: The relationship between cerebral ischemia and oxidative stress.
Note: ATP: Adenosine triphosphate; COX: cyclooxygenase; nNOS: neuronal nitric oxide synthase; NO: nitric oxide; ROS: reactive oxygen species.

Excitotoxicity

When ischemia/reperfusion injury occurs, calcium overload-induced free radical quenching in brain cells may be one of the mechanisms of sevoflurane posttreatment against oxidative stress-induced neurotoxicity. NAD(P)H quinone oxidoreductase 1, has the ability to eliminate superoxide anion radicals and prevent the formation of reactive oxygen species.[45] Some studies have shown that activation of the phosphatidylinositol 3-kinase/serine-threonine protein kinase signaling pathway can upregulate the expression of NQO1 in ischemic brain tissue, while sevoflurane post-treatment can activate the PI3-K/Akt pathway.[46] Therefore, sevoflurane post-treatment can upregulate the expression of NQO1 in ischemic brain tissue by activating the PI3-K/Akt pathway, thus playing a role in brain protection.

Inflammatory Reaction

Brain inflammation is closely related to the occurrence and development of ischemic brain injury.[47] Transcription factors such as nuclear factor kappa B can regulate the expression of inflammatory genes.[48] Nuclear factor kappa B is the first responder to the stimulation of harmful cells. It is mainly activated in neurons. It induces several proinflammatory cytokines. Sevoflurane preconditioning may reduce the activation of nuclear factor kappa B, and then downregulate the expression of nuclear factor kappa B dependent inflammatory genes. Therefore, it can directly inhibit the inflammatory response caused by cerebral ischemia, thereby reducing the infarct volume of focal cerebral ischemia in rats and reducing the neurological deficit.[49]

Apoptosis

Apoptosis is also an important mechanism of cell death after cerebral ischemia/reperfusion. E2F transcription factor 1/enhancer of zeste homolog 2/tissue inhibitor of metalloproteinases-2 regulatory axis can promote neuronal apoptosis. Sevoflurane can reduce apoptosis of hippocampal neurons

in rats with cerebral ischemia/reperfusion injury by down-regulation of E2F1 and activation of ezh2 mediated TIMP2 inhibition, thus playing a brain protective role in ischemia/reperfusion injury (**Figure 3**).[50]

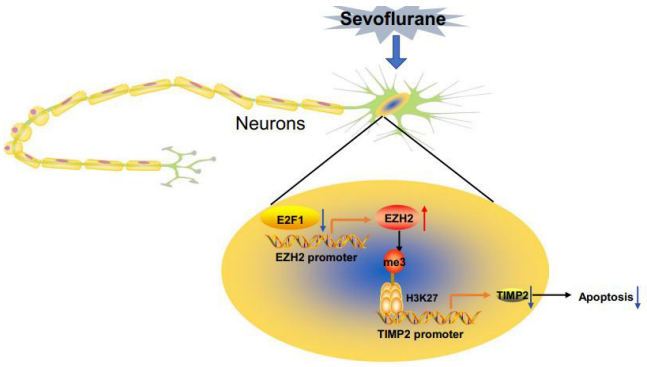

Figure 3: The mechanism of sevoflurane inhibiting cell apoptosis.
Note: E2F1: E2F transcription factor 1; EZH2: enhancer of zeste homolog 2; TIMP2: tissue inhibitor of metalloproteinase-2.

Others

After cerebral ischemia/reperfusion injury, the branched microglia/macrophages of sevoflurane pretreated rats rapidly transformed into amoeba like morphology and accumulated in the infarcted cortex and striatum, indicating that sevoflurane enhanced the phagocytosis efficiency by increasing the phagocytosis of each cell.[51] Sevoflurane preconditioning has neuroprotective effects. It can not only accelerate the spatio-temporal dynamics of astrocytes, but also provide astrocyte scaffolds for the migration of neuroblasts to ischemic regions, and promote neural reconstruction after cerebral ischemia.[52]

Characteristics of sevoflurane preconditioning and postconditioning

Sevoflurane has an active role in cerebral infarction, especially in ischemic cerebral infarction. At present, it is known that it can treat ischemia/reperfusion injury after ischemic cerebral infarction through preconditioning and postconditioning. However, preconditioning is clinically feasible only when the occurrence of cerebral ischemia is predictable. In reality, the most common cerebral ischemia often occurs outside the hospital and is unpredictable. Therefore, compared with preconditioning, postconditioning has a broad application prospect and can be applied after cerebral ischemia. The concept of ischemic postconditioning was introduced in 2003. At that time, it was proposed to improve the cardiac outcome after ischemia. Later, people began to study its positive role in brain injury. However, the number of studies on sevoflurane postconditioning is still relatively small. It is still necessary to continue to study and explore the effects of sevoflurane postconditioning on cerebral ischemia/reperfusion injury after stroke (especially ischemic stroke).

Dose

2–7% sevoflurane is considered sufficient to reduce the infarct volume, while 1% is insufficient.[53-55] 4% sevoflurane leads to hypercapnia at the end of preconditioning. At the same time, sevoflurane may cause respiratory depression and hypotension, which may affect its preconditioning effect. Ye et al.[56] measured arterial blood gas and physiological variables during preconditioning with 2.4% sevoflurane, and there was no respiratory depression and hypotension during the whole experiment. Therefore, based on the existing research, we can temporarily conclude that the theoretical optimal concentration of sevoflurane preconditioning is about 2.4%.

Conclusion

As a new anesthetic, sevoflurane preconditioning and postconditioning have been shown to have a beneficial effect on stroke in various studies. This paper, through the summary and analysis of previous studies on the positive role of sevoflurane in stroke, reveals that sevoflurane can intervene in the ischemic reperfusion injury events after stroke (mainly ischemic stroke) by means of preconditioning and postconditioning. Based on the relevant mechanisms, we can obtain the corresponding brain protection and improve the prognosis. Therefore, we can speculate that sevoflurane may play an irreplaceable role in the treatment of stroke in the future, and has relatively broad prospects (**Table 1**).

Author contributions
JX and YY were responsible for writing the manuscript and literature retrieval. WL was responsible for review design and manuscript revision. HS and GC were responsible for manuscript drafting and revision. All authors read and approved the final version of the paper for publication.
Conflicts of interest
The authors declare that they have no competing interests.
Editor note: GC is an Editorial Board member of *Medical Gas Research*. He was blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and his research group.

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Table 1: Main citation summary

Study	Year	Results
Dang et al.[51]	2022	Sevoflurane enhances phagocytic efficiency by increasing the phagocytic capacity of each cell
Yang et al.[50]	2022	E2F1/EZH2/TIMP2 regulatory axis can promote neuronal apoptosis. Sevoflurane can protect brain from ischemia/reperfusion injury by down regulating E2F1
Yu et al.[52]	2019	Sevoflurane can provide astrocyte scaffold for the migration of neuroblasts to ischemic regions, and promote neural reconstruction after cerebral ischemia
Yang et al.[16]	2016	Sevoflurane is safe, fat soluble, and highly permeable to the blood-brain barrier, which is crucial for delivery to the brain
Shah et al.[4]	2015	Stroke is mainly due to the aging of the population in high-income countries and the accumulation of stroke risk factors in low - and middle-income countries, such as smoking, hypertension and obesity
Li et al.[46]	2014	Sevoflurane post-treatment can up regulate the expression of NQO1 in ischemic brain tissue by activating PI3-K/Akt pathway, thus playing a role in brain protection.
Rodrigo et al.[35]	2013	Antioxidant methods play an obvious role in protecting the brain from various kinds of damage
Liu et al.[41]	2012	Sevoflurane post-treatment can protect against cerebral ischemia/reperfusion injury by regulating the activity of brain antioxidant enzymes
Wang et al.[49]	2011	Sevoflurane preconditioning may reduce the activation of NF kappa B, and then down regulate the expression of NF kappa B dependent inflammatory gene, thereby directly inhibiting the inflammatory response caused by cerebral ischemia, thereby reducing the infarct volume of focal cerebral ischemia in rats and reducing the neurological deficit
Chong et al.[34]	2005	Antioxidant methods play an obvious role in protecting the brain from various kinds of damage

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