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Volatile anesthetics and ischemia-reperfusion injury

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Ischemia-reperfusion (IR) injury can occur under various clinical conditions in which the restoration of blood and oxygen to ischemic tissues results in a massive release of oxygen free radicals. For example, cardiac surgery, stroke, tourniquet application for orthopedic surgery, organ transplantation, and restoration of shock can cause IR injury. Reperfusion produces an increased free radical concentration with lipid peroxidation, microvascular injury, inflammatory cytokine release, and neutrophil activation. In addition, IR stress triggers necrotic or apoptotic cell death. Understanding the mechanisms of IR injury may provide therapeutic targets to decrease IR injury and improve outcomes in clinical settings (e.g., coronary or cerebral vascular disease). Some anesthetic agents, including volatile or intravenous anesthetics, are known to have a protective effect against IR injury. The guidelines of the American College of Cardiology and the American Heart Association recommend volatile anesthetic agents during non-cardiac surgery for the maintenance of general anesthesia in hemodynamically stable patients at risk for myocardial ischemia [1].

Several mechanisms have been proposed to explain the protective effect of volatile anesthetics against cardiac IR injury. IR can increase neutrophil adhesion to vascular endothelial cells, which contributes to reperfusion injury. Volatile anesthetics such as isoflurane and sevoflurane can reduce the reperfusion-induced adhesion of neutrophils at clinically relevant doses [2]. Volatile anesthetics are known to improve adenosine triphosphate (ATP) synthesis and decrease the production of reactive oxygen species, which are associated with reduced rates of respiration and phosphorylation in the electron transport chain and ATPase activity in mitochondria. The positive effects of volatile anesthetics are also associated with mitochondrial ATP-sensitive K^+ channel opening, which leads to a decrease in postischemic intracellular Ca^{2+} concentrations [3].

Volatile anesthetics are known to diminish cerebral IR injury. Neuroprotective effects of volatile anesthetics have been shown in various *in vitro* and *in vivo* experimental models. In this issue of the *Korean Journal of Anesthesiology*, Kim et al. [4] report that isoflurane post-treatment provides neuroprotection against tissue plasminogen activator (tPA)-exaggerated brain IR injury. In this study, isoflurane improved neurobehavioral function and decreased the cerebral infarct volume and intracranial hemorrhage induced by tPA-exaggerated brain IR injury. Although tPA is an effective intervention for the treatment of acute ischemic stroke, it has various detrimental effects on brain IR injury, including hemorrhagic transformation, cytotoxicity, increased microvascular permeability, and neutrophil degranulation with the release of matrix metalloproteinase (MMP)-9, neutrophil elastase, and myeloperoxidase [5]. As discussed in this issue of the *Korean Journal of Anesthesiology*, the downregulation of MMP-9 is a plausible mechanism for the protective effect of isoflurane. Volatile anesthetics, including isoflurane and sevoflurane, are known to increase survival signaling such as PI3K/Akt signaling, which is involved in the protective effect of anesthetics against cerebral IR injury. Recent studies have shown that isoflurane post-conditioning decreased the infarct volume, number of apoptotic cells, and neurological deficits 4 weeks after middle cerebral artery occlusion-induced ischemic brain injury. Isoflurane reduced IR-induced nuclear transcription factor-κB activation, interleukin (IL)-1β, and IL-6 in the penumbral area [6]. These results suggest that the anti-inflammatory effect of isoflurane is also involved in the neuroprotective effect.

Numerous studies have shown that various anesthetic agents can decrease cerebral IR injury. As described in this issue of the *Korean Journal of Anesthesiology*, isoflurane is a promising anesthetic agent in ischemic brain injury. IR injury is unavoidable in clinical situations, and anesthesia is necessary for surgical practice. Therefore, determining the optimal anesthetic modality is important to improve clinical outcomes.

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