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Is there a place for sevoflurane to prevent liver ischemia-reperfusion injury during liver transplantation?

Estela Regina Ramos Figueira, Joel Avancini Rocha Filho

Volatile anesthetics have been widely used to perform general anesthesia. In the last years, non-anesthetic properties of these drugs appeared to provide additional benefit in conditions related to ischemia and reperfusion of various organs. As far back as 1983, protection from ischemia was evaluated as a novel attribute from volatile anesthetics (VA) that commenced to be explored [1]. After that new evidences pointed that pharmacological conditioning with the VA isoflurane, sevoflurane and desflurane could be a new strategy easily applicable to protect organs from ischemia. Therefore, numerous studies established that VA prevents myocardial injury from ischemia. In this scenario, in 1989, Kashimoto et al. [2] found that isolated rat hearts exposed to sevoflurane showed increased myocardial ATP levels in the postischemic state, indicating cardioprotection. This finding is in agreement with experimental [3, 4] and clinical studies [5, 6] developed later that reinforced the cardioprotective properties of VA. However, some studies have failed in demonstrating non-anesthetic beneficial effects from VA compared to intravenous anesthetics such as propofol [7, 8]. These conflicting results can be in part explained by differences in the protocols of VA application. Some studies applied continuous VA protocols, while others applied VA for short periods, during ischemia or during reperfusion, with or without drug washout. [9] So, it is rational to think that the cardioprotective effect can change with the change in VA administration protocol.

It has been recognized that isoflurane, sevoflurane and desflurane may prevent ischemia-reperfusion (IR) injury through similar molecular pathways. The protective mechanisms of pharmacological conditioning with VA are not fully understood, but it appears to involve multi-pathways that may be initiated before ischemia (preconditioning) or during reperfusion (post-conditioning). According to the current literature, the protective mechanisms of anesthetic preconditioning (APC) against IR injury are similar to the mechanisms related to ischemic preconditioning (IPC). In both cases, the opening of mitochondrial ATP sensitive potassium channels ($mitoK_{ATP}$) is a key mediator of protection. In normal conditions the $mitoK_{ATP}$ is closed in inactive form. During ischemia the decrease in ATP concentrations result in opening of $mitoK_{ATP}$, with consequent decrease in Ca^{2+} overload into mitochondria. In fact, it was showed that VA prime the $mitoK_{ATP}$ to open at minor decreases in ATP levels via protein kinase C signaling [10]. This allows production of mitochondrial ATP for an extended time during the ischemic period, reducing accumulation of degraded ATP into mitochondria. It has been demonstrated that sevoflurane preconditioning as well post-conditioning occur via $mitoK_{ATP}$ opening, decreasing IR injury in models of heart ischemia and cerebral ischemia [11, 12]. This indicates that $mitoK_{ATP}$ play a role in the mechanism of VA protection not related to the period of drug administration, before ischemia or during reperfusion.

It is consensus that mitochondria play a central role in cell death, being decisive in the development of IR injury. More recently, it has been showed that mitochondrial permeability transition pore (mPTP) is another mediator of VA pre- and post-conditioning protection from organ ischemia [13, 14]. The mPTP is a large channel of the inner mitochondrial membrane that typically opens during oxidative stress. Opening of mPTP allows entrance of water and solutes into the mitochondria, causing massive matrix swelling, breakdown of mitochondrial membrane potential, and

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Received: 25 May 2015
Published: 06 July 2015

loss of small components like cytochrome c, contributing to cell death, i.e., IPC can suppress the opening of mPTP protecting from the heart against IR injury [15]. Isoflurane and sevoflurane increases phosphorylation of glycogen synthase kinase 3-beta (GSK3β), leading to inhibition of mPTP opening during reperfusion as it occurs during IPC [13]. Additionally, conditioning with sevoflurane may play a role in preserving microcirculation. Anneck et al. suggested sevoflurane decreases degradation of endothelial glycocalyx after IR possibly through a mechanism that involves a decrease in release of lysosomal cathepsin B, in a model with isolated guinea pig hearts [16].

Sevoflurane has shown protection against IR injury in other situations than heart ischemia, such as cerebral [17], intestinal [18], renal [19] and liver ischemia [20]. In the setting of liver transplantation (LT) and surgery, several strategies have been systematically tested with the objective to reduce liver IR injury [21–23]. During surgical resection the liver is subject to ischemia when Pringle's Maneuver [24] is applied to reduce parenchymal bleeding. To protect the liver against IR injury two strategies have been clinically accepted, being then, IPC and intermittent vascular occlusion (IVO). Thus, a pharmacological approach looks an attractive simple and safe alternative than the additional surgical procedures. Up to now, there are not many studies showing the effects of sevoflurane on liver injury. Bedirli et al. [25] demonstrated reduced liver injury when rats were exposed to 2% sevoflurane compared to 1.5% isoflurane, using a model of hepatic IR injury. They found increased adenosine triphosphate (ATP) and energy levels with significant recovery of blood flow in the sevoflurane group after 45 minutes of liver ischemia. In the same year, Beck-Schimmer et al. [20] published a randomized controlled trial (RCT) showing that sevoflurane preconditioning during liver resection decreases liver injury and improves outcome. The aspartate transaminase (AST) peak level was significantly decreased in the sevoflurane group compared to the propofol. Additionally, inducible nitric oxide synthase expression was up-regulated during reperfusion in the sevoflurane group, indicating a possible role of nitric oxide (NO) in VA protection. NO is a signaling molecule involved in the activation of mitoK_{ATP} via protein kinase C pathway [26]. Later, in a second RCT, Beck-Schimmer et al. [27] demonstrated that sevoflurane post-conditioning is comparable to IVO during liver surgery, showing decreased levels of AST and better clinical outcome in both groups compared to patients without any intervention to protect from liver IR injury. A more recent RCT showed comparable results in severity of liver injury and outcome, comparing among IPC, sevoflurane preconditioning and IVO (control group) [28]. Well, because IVO is also a strategy to prevent liver ischemia and clinical complications after liver surgery, it is not surprising that the IVO group presented similar results to the IPC and sevoflurane groups. A meta-analysis published recently showed IPC is not superior to IVO when analyzing outcome after liver resection [29]. On the other hand, a prospective clinical study with 227 patients included did not show any protection from liver IR injury with continuous sevoflurane conditioning during hepatic resection compared to propofol continuous infusion [30]. In a previous randomized study with one hundred patients included, Song et al. [31] also did not found differences between groups, comparing sevoflurane conditioning to propofol during hepatectomy.

With respect to LT, there are few studies evaluating sevoflurane protection from liver IR. Kong et al. [32] showed better results with sevoflurane compared to chloral hydrate anesthesia in a model of small-size LT in rats. Although there were no differences in the levels of liver transaminases between groups, the sevoflurane group presented decreased inflammation, decreased oxidative stress, and better renal function with decreased creatinine levels. A more recent experimental study, using a model of LT in rats, compared sevoflurane to isoflurane exposure showing decreased transaminases levels analyzed in the liver graft preservation fluid, and increased NO concentrations in liver tissue samples after LT surgery [33]. Despite these encouraging results, it is not certain if these properties of VA can be applied to the clinical setting. A randomized clinical study in LT, with sevoflurane preconditioning applied to the deceased donor, demonstrated that sevoflurane preconditioning decreases the incidence of early graft dysfunction, particularly in the subgroup of patients that received grafts with moderate steatosis [34]. Conversely, in a very recent multicenter RCT in LT, sevoflurane post-conditioning compared to propofol did not prevent acute liver injury, but indicated incidence of less severe complications in the sevoflurane group [35].

LT and hepatic surgery still require careful attention during perioperative care of patients with liver dysfunction. In the operating room, the anesthetic choice can be challenge and in some occasions may affect outcome particularly of LT patients. Certain anesthetics such as sevoflurane and isoflurane may provide hepatic protection from liver IR injury. Nevertheless it is our understanding that further research is required to define better the role of VA protection in liver surgery and transplantation.

How to cite this article

Figueira ERR, Filho JAR. Is there a place for sevoflurane to prevent liver ischemia-reperfusion injury during liver transplantation? Edorium J Anesth 2015;5:1–5.

Article ID: 100001A05EF2015

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doi:10.5348/A05-2015-1-ED-1

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Author Contributions

Estela Regina Ramos Figueira – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Joel Avancini Rocha Filho – Substantial contributions to conception and design, Drafting the article, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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