

The Anesthesiologist's Expanding Role in Perioperative Liver Protection

A few decades ago, liver surgery was a highly hazardous undertaking. In the 1960s, the rate of perioperative mortality after liver resection was up to 50%.¹ Substantial progress in surgery and perioperative care has made liver surgery dramatically safer, with a current mortality rate lower than 1% in patients with normal preoperative liver function. Surgical strategies have evolved considerably, thanks to a better knowledge of liver anatomy and pathophysiology. The use of vascular clamping to minimize blood loss, and more recently the adoption of strategies for manipulating liver volume, such as preoperative embolization and the preservation of remaining liver cells, make it possible to perform extensive resections with low perioperative mortality and morbidity.² The contribution of anesthesiologists to these developments deserves to be highlighted. Initially, anesthesiologists focused on the management of intraoperative massive hemorrhage and blood transfusion. Thereafter, they actively contributed to the development of hepatic vascular clamping through the understanding and appropriate management of the resulting intraoperative hemodynamic instability.³ We are currently facing a new challenge because of growing evidence that our choice of anesthetic plays a role in liver protection. In this issue of *ANESTHESIOLOGY*, Yang *et al.*⁴ provide evidence for a protective effect of remifentanyl preconditioning against ischemia–reperfusion injury in rat livers. Such protective effects of opioids,⁵ and remifentanyl in particular,⁶ have been extensively demonstrated in the myocardium.

Warm ischemia of the liver occurs during a variety of clinical situations such as trauma, shock, and liver surgery. It rapidly leads to sinusoid endothelial cell damage and hepatocyte necrosis.⁷ Reperfusion then activates Kupffer cells, thereby inducing inflammation and the production of reactive oxygen species that may seriously impair liver function and its ability to regenerate after resection, especially in patients with abnormal preoperative liver function.²

Preconditioning refers to the strategies that could prepare an organ for ischemic conditions by triggering natural cell defenses.^{7,8} Clavien *et al.*² demonstrated that ischemic preconditioning (a brief period of ischemia followed by a short interval of reperfusion before prolonged ischemia) was effective in minimizing postoperative hepatocyte injury. Halogenated anesthetic agents appear to mimic the ischemic preconditioning effect. In a randomized clinical controlled trial, preconditioning with halogenated anesthetic agents, administered for 30 min before inflow liver occlusion, was associated with a significant reduction in liver enzymes and post-

operative morbidity in comparison with propofol-based anesthesia.⁹ The choice of anesthetic agents during liver surgery therefore may be of great consequence.

In the study by Yang *et al.*,⁴ different concentrations of remifentanyl were administered for 15 min and stopped 10 min before induction of a 45-min period of ischemia. One hundred twenty minutes after reperfusion, the authors observed a significant reduction of morphologic and biologic markers of hepatic ischemic injury in the rats having received a remifentanyl infusion in comparison with the control group. Thereafter, the authors attempted to explore the mechanisms of remifentanyl-induced liver protection. By using combinations of agonist-antagonists, they showed that remifentanyl preconditioning could at least be partly ascribed to a release of nitric oxide secondary to an activation of inducible nitric oxide synthase (iNOS), and that this effect was independent of the activation of opiate receptors. Interestingly, the authors completed their investigations with the assessment of *in vitro* isolated hepatocytes exposed to hypoxia and reoxygenation. The authors found that remifentanyl consistently improved the viability of hepatocytes, with this effect being inhibited by nitric oxide antagonists but not by naloxone, an opioid antagonist.

Yang *et al.*⁴ have to be congratulated for this well-documented and fruitful study of liver protection by opiates. Several points need to be raised. Regarding clinical relevance, it should be noted that the protective effect was only observed with high doses of remifentanyl (at least $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the *in vivo* set of experiments, and the maximal effect was obtained at a $10 \text{ ng} \cdot \text{ml}^{-1}$ concentration in the *in vitro* set of experiments). Extrapolation of these values to the clinical setting is difficult because pharmacologic parameters (for example, protein binding, diffusion volume, and clearance) differ between rats and humans. Notwithstanding, these doses and concentrations correspond to those commonly used in other studies on organ protection, and seem relatively close to the upper range of clinical use. Other modalities of administration, and the interest of infusing remifentanyl afterward (postconditioning), require further investigation. Another important clinical point that deserves additional study is whether remifentanyl exerts similar protective effects in the diseased liver.

As in other studies on organ protection, the hypoxic origin of the reported lesions could have been more firmly dem-

Accepted for publication December 30, 2010. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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◆ This Editorial View accompanies the following article: Yang L-Q, Tao K-M, Liu Y-T, Cheung C-W, Irwin MG, Wong GTC, Lv H, Song J-G, Wu F-X, Yu W-F: Remifentanyl preconditioning reduces hepatic ischemia–reperfusion injury in rats *via* inducible nitric oxide synthase expression. *ANESTHESIOLOGY* 2011; 114:1036–47.

onstrated. This is probably especially important in this context, because liver manipulation during surgical preparation is likely to promote cell death, inflammation, and liver dysfunction.¹⁰ This question is further complicated by the fact that vascular supply to the liver arises from distinct multiple vessels in rats. To address this question, it would have been interesting to compare the lesions observed in the hepatic lobes subjected to vascular deprivation with those in non-ischemic areas of the liver.

Regarding the mechanisms of action, the relative role of different NOS isoforms needs to be further specified in the future. The authors' assumption that iNOS rather than constitutive endothelial nitric oxide synthase (eNOS) is up-regulated during preconditioning is in sharp contrast with previous observations after ischemic preconditioning. It is widely accepted that after liver ischemia–reperfusion, eNOS is rather protective, whereas iNOS induction may contribute to hepatic injury.¹¹ Some differences in the respective implications of NOS isoforms could be related to the timing of evaluation. The authors looked at immediate reperfusion injury only, and their conclusions might have been different if they had focused on later reperfusion time points.

Similarly, the assumption of a mechanism of action independent of the activation of opiate receptors remains questionable and is at odds with our knowledge of the cardioprotective effects of opiates, especially remifentanyl, with a clear involvement of δ - and κ -opiate receptors.^{5,6} In the current study, naloxone was administered well before the induction of ischemia rather than concomitantly with remifentanyl. Considering its short half-life, the residual concentrations of naloxone at the time of remifentanyl infusion and ischemia are questionable and may explain some discrepancies.

Finally, the protective effect of remifentanyl against *in vitro* isolated cultured hepatocyte injury raises the question of the respective implication of different lineages of hepatic cells (hepatocytes and Kupffer cells) in the process of liver preservation. As in the setting of myocardial preservation,⁵ the observations by Yang *et al.*⁴ on *in vitro* isolated hepatocytes makes one wonder whether opiates should be a component of cold storage solutions used to preserve liver grafts before transplantation.

Liver surgery is still moving toward better efficacy and safety. The recent development of modern surgical tools (such as ultrasonic dissectors and bipolar coagulation), as well as a tight control of intraoperative central venous pres-

sure by anesthesiologists, has made systematic vascular clamping questionable.¹² Regardless, the liver is still subjected to ischemia in numerous circumstances and the study by Yang *et al.*⁴ provides evidence that anesthesiologists, through their choice of anesthetic drugs, may contribute to protection of the liver.

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