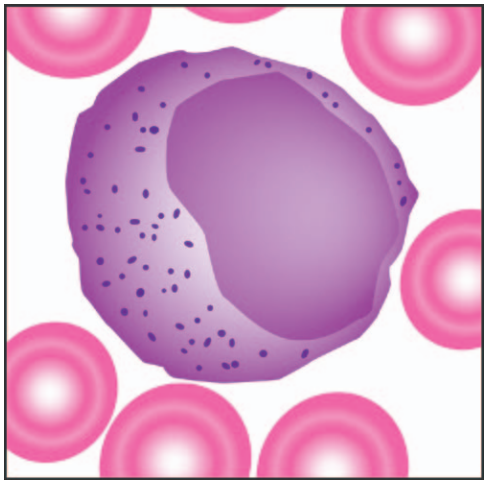
Sleeping to Survive?

The Impact of Volatile Anesthetics on Mortality in Sepsis

TO the clinician, volatile anesthetics are the means by which we render patients insensitive to pain, still, and unaware/amnestic. To the molecular pharmacologist, they are the object of an ongoing search for mechanism(s) of action. To the laboratory investigator, they are a tool for rendering animals anesthetized in order to perform various experimental procedures. From a clinical perspective, we often view volatile anesthetics and their effects as benign, reversible, and temporary. Or are they?



"[This study] raises the possibility that unique anesthetics given at different times could potentially alter the host immune response thereby improving survival [in sepsis]."

In this issue of ANESTHESIOLOGY, Herrmann *et al.*[1] report the effects of volatile anesthetics in a murine model of sepsis. They used a common approach, cecal ligation and puncture (CLP), in which the cecum is tied off and punctured with a needle in a standard manner so as to leak intestinal contents into the peritoneum, which then causes sepsis in a reproducible model. Animals were anesthetized during surgery and for 2 h postoperatively with 1.2 minimum alveolar concentration of desflurane, isoflurane, or sevoflurane (termed "conditioning" by the authors). A sham (control) group of animals underwent laparotomy with ketamine anesthesia without CLP. Outcome assessments included 7-day survival, renal and hepatic function, bacterial load in blood and peritoneal fluid, and cytokine concentrations in plasma and peritoneal fluid. In a second series of experiments, the original CLP was performed with ketamine anesthesia, and the animals were anesthetized 24 h later with sevoflurane or desflurane, to determine the effects of volatile anesthetics after initiation of sepsis (termed "postconditioning" by the authors).

When administered using the first (conditioning) regimen, 7-day survival significantly increased from 17% in controls to 83 and 58% after sevoflurane and desflurane, respectively, but was not significantly increased by isoflurane (42%). When administered 24 h after CLP (postconditioning), sevoflurane (1 minimum alveolar concentration for 0.5 h) significantly increased survival to 66%, but neither desflurane (1 minimum alveolar concentration for 0.5 h) nor a greater sevoflurane exposure (1.2 minimum alveolar concentration for 2 h) increased survival. In the first experiment, sevoflurane partially prevented renal and hepatic dysfunction (evidenced by lesser increases in blood urea nitrogen and hepatic enzymes such as transaminases). It did not reduce bacterial load in peritoneal fluid and blood or alter levels of interleukin-6 or monocyte chemoattractant protein-1 in plasma and peritoneal fluid.

The ability of sevoflurane to modulate sepsis-induced organ injury and survival, whether given during CLP and for 2 h afterwards or when given at a lower dose for 30 min 24 h post-CLP exposure, is interesting. So also is the ability of desflurane during CLP and for 2 h afterwards (but not at 24 h), and the lesser ability of isoflurane using the same strategy. And with these new observations come the natural questions: (1) what is the mechanism, (2) why are the anesthetics different with regard to their conditioning effects, and (3) why is sevoflurane but not desflurane effective in a postconditioning regimen? Unfortunately, the report by Herrmann *et al.* raises more questions than it answers.

Given that animal mortality in sepsis is highly dependent on both sex and strain, it is unclear whether these results would be generalizable to either female mice or either outbred or other commonly used inbred strains. There is also increasing recognition that mortality continues up to 28 days after CLP,[2] and the impact of volatile anesthetics on late deaths from sepsis was not evaluated in the experiments

Illustration: J. P. Rathmell.

Accepted for publication June 19, 2013. Funding was provided by National Institutes of Health (Bethesda, Maryland) Grants R01-DA14211 and R01-DA02931 (to Dr. Kharasch); R01 GM072808 and R01GM104323 (to Dr. Coopersmith).

 Anesthesiology 2013; 119:755-6

◆ This Editorial View accompanies the following article: Herrmann IK, Castellon M, Schwartz DE, Hasler M, Urner M, Hu G, Minshall RD, Beck-Schimmer B: Volatile anesthetics improve survival after cecal ligation and puncture. ANESTHESIOLOGY 2013; 119:901–6.

reported by Herrmann *et al*. Furthermore, the investigators did not give animals postoperative antibiotics, a common practice after CLP in order to enhance clinical relevance. It is known that antibiotics improve survival after CLP, and it is not clear whether the survival advantage conferred by volatile anesthetics would persist in either a lower mortality model or one with a lower bacterial burden. It is also questionable whether the modest differences in blood urea nitrogen and transaminases are sufficient to account for the profound survival advantage conferred by sevoflurane, especially given the absence of differences in bacteremia, local infection, or proinflammatory cytokines. Sepsis is associated with chronic immunosuppression and modulating the immune system represents a potential therapeutic avenue in the disease. Given the fact that volatile anesthetics can have immunomodulatory effects, assaying the immune system represents a logical next step. In addition, the investigators only evaluated biochemical outcomes after sevoflurane but not isoflurane or desflurane exposure, and not when started 24 h after CLP. They also did not evaluate differences between the drugs. Are desflurane and isoflurane less effective because they undergo less metabolism?[3]

We also do not know whether the effects of differing anesthetics are additive. This is possible in light of a recent study of two different models of critical illness examining the impact of giving ketamine before the induction of sevoflurane anesthesia.[4] Survival was improved in mice that received ketamine 10 min before anesthesia with sevoflurane that were given a lipopolysaccharide challenge immediately after laparotomy compared with mice given sevoflurane alone although ketamine had no impact on survival in mice given *Escherichia coli* after a laparotomy. This study design differed from that of Herrmann *et al.* in both the anesthetic strategies and models of critical illness used; however, it raises the possibility that unique anesthetics given at different times could potentially alter the host immune response thereby improving survival.

Although a number of questions remain, we can now add the survival benefit conferred by sevoflurane and desflurane after CLP to previous examples of protection by volatile anesthetics against injury from cerebral, cardiac, hepatic, and renal ischemia–reperfusion, and by isoflurane against a comparable model of CLP sepsis.[5] A mechanistic understanding of how volatile anesthetics improve rodent survival in models of sepsis and ischemia–reperfusion may thus yield new exciting therapeutic avenues to pursue in critically ill patients. And additionally, mechanistic questions aside, and of immediate relevance to experimentalists using volatile anesthetics to enable their animal procedures, is that these drugs may not be the benign, temporary, and reversible tools they might be considered to be. As identified by Herrmann *et al.*, anesthesia may be a critical confounder when comparing study data where different anesthetic protocols were used.

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