Xenon and Cardioprotection

Is This the Light at the End of the Tunnel?

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ALTHOUGH the anesthetic effect of xenon was discovered more than 60 yr ago,[1] it is better known for automotive headlight applications than for use in the operating theatre. In this issue of Anesthesiology, Hofland *et al.*[2] report the largest ever conducted evaluation of the cardioprotective properties of xenon in cardiac surgery patients.

The use of xenon in routine anesthesia has been limited by high price and low availability. The global production of this noble gas by a fractional distillation process of liquid air consumes an enormous amount of energy and would not cover for more than few days of the anesthesia procedures conducted worldwide every year.

Xenon has a minimum alveolar concentration of about 60% and requires specialized anesthesia machines with closed circuits (*i.e.*, only the oxygen consumed by the patient is replaced in the circuit) to limit the volume needed. Any accidental unplugging, or flushing, of the circuit would have a dramatic impact on the anesthesia cost. Overall, an optimal xenon anesthesia requires about 20 l for 2 h, and the cost ratio compared to other anesthesia agents (*i.e.*, sevoflurane, isoflurane, propofol) ranges from 3 to 10.

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Xenon is an expensive anesthetic drug, but interest in using it persists because of cardio- and neuroprotective properties demonstrated in animal models. Such properties in humans could support the cost difference. Hofland *et al.*[2] conducted an international, 17-center randomized trial to estimate cardioprotective effects of the xenon in low-risk cardiac surgery. In total, 492 patients were randomized to receive xenon (n = 161), sevoflurane (n = 165), or propofol-based total intravenous anesthesia (TIVA, n = 166) for anesthesia maintenance. The primary outcome was troponin concentration measured at 24 h postoperative. Xenon was found to be noninferior but not superior to sevoflurane (P = 0.01 and P = 0.32, respectively). Xenon but not sevoflurane was superior to TIVA (P = 0.05 and P = 0.33, respectively). These results support the hypothesized cardioprotective effects of the xenon in this clinical setting. The apparent discrepancies in the presented results (*i.e.*, xenon and sevoflurane are not different, but xenon is superior to TIVA) are easily explained by the small sample size and the relatively low statistical power to detect differences between groups. Larger trials, or trials with less experimental groups, would likely demonstrate significant differences. In fact, the xenon group presented a lower peak of troponin releases (P = 0.09) than the other groups. Would this difference be significant (P < 0.05) if the authors had chosen a two-arm design?

Several studies have demonstrated an association between the magnitude of postoperative troponin release and the postoperative mortality after cardiac or noncardiac surgery.[3] However, the choice of postoperative troponin level as the primary outcome raises two concerns. First, we must remember that postoperative troponin release cannot be considered as a surrogate outcome; *i.e.*, an easy-to-measure marker that is interchangeable with a real clinical outcome of interest to evaluate the treatment effect. For example, in a large randomized control trial conducted in noncardiac surgery,[4] it has been shown that an intervention decreasing

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postoperative cardiac complications actually increased 30-day mortality. When at least one intervention (appropriate or not) breaks the link between an intermediary outcome and 30-day mortality, its use as a surrogate is no longer appropriate, and assumptions about the clinical benefits of a decrease of an intermediary outcome (*e.g.*, troponin release) should be interpreted with extreme caution. However, even if troponin release cannot be considered as a surrogate outcome for 30-day mortality, it remains reassuring to observe that xenon is associated with decreased postoperative troponin releases after low-risk cardiac surgery.

Second, the minimal clinically important difference for this low risk population is not well understood. Although the difference observed between xenon and sevoflurane and TIVA reached statistical significance, the clinical importance is unclear. Achieving statistical significance means that the observed differences in troponin release magnitudes are not likely related to chance, with the limitation associated with small sample size randomized control trials.[5] However, the results do not inform us about the clinical impact of the observed treatment effects. The prognostic value of postoperative troponin releases after cardiac surgery is well established, but the quantification of absolute changes is not established. When comparing the average peak values in the xenon and in the propofol groups, the difference is about 10 μg/l. The only predictive model using a similar troponin test suggested that such a difference would be associated to a relative increase of 1-yr mortality ranging from 3 to 20%. Although a treatment effect of this magnitude would be exciting, we must recognize that nothing validates that these models were well calibrated in this range of observed postoperative troponin releases. A more transparent interpretation should recognize that despite the significant decrease of postoperative troponin release that was observed, the impact of the reduced troponin concentration on clinical outcome is uncertain.

The study monitoring included a follow-up to evaluate the safety of the use of xenon in cardiac surgery. The results are reassuring, and nothing suggested that xenon is unsafe; however, definite claims about safety cannot be drawn on 161 exposed patients. Severe complications in this low-risk cardiac surgery population were not frequent. In this study, the power to detect differences for adverse events observed in 1 to 3% of the case is almost null. Although the shorter intensive care unit (ICU) and hospital stay in the xenon group is interesting information, it is potentially influenced by other factors influencing patient transfer out of the ICU.

Although the present study does not provide definitive evidence regarding the clinical cardioprotective effect and safety of xenon in low risk cardiac surgery, the presented results are more than encouraging and deserve further studies to determine the role of this gas in cardiac surgery. Xenon is an anesthetic agent, and we therefore assume that the dose needed to induce a cardioprotective effect is the same as the one required to induce anesthesia. This assumption is not well supported by evidence. Lower doses may produce similar cardioprotective effects. Switching the focus of xenon administration from an anesthetic agent to a cardioprotective therapy would have a major impact on cost considerations.

The study of Hofland *et al.*[2] confirms that xenon reduces troponin release compared to TIVA after cardiac surgery. Although definitive conclusions about the safety of xenon and its impact on clinical myocardial outcomes can be debated, one must recognize the tremendous amount of work reported in this publication. The Xenon-CABG Study Group should be congratulated for completing this trial in cardiac surgery patients. Whether we should or should not start using it in cardiac surgery remains uncertain, but this study is a step forward in understanding the potential for xenon use in anesthesia.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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