Anesthetics and Lung Injury

Old Research, New Insights

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THESE days anesthesiologists read a lot about serious problems potentially caused by anesthetics, such as postoperative cognitive dysfunction or long-term neurologic impairment in children[1]; thus, it makes a refreshing change to see when a commonly used anesthetic has benefit beyond providing anesthesia. In this issue of ANESTHESIOLOGY, Englert *et al.*[2] report that isoflurane reduces lung injury caused by sepsis and mechanical ventilation, and it does so by protecting the integrity of the alveolar–capillary barrier.

This is certainly not the first demonstration that anesthetics can protect against organ injury. Such investigations have been reported for over 5 decades,[3] and have shown among other effects, that anesthetics can be antiinflammatory, induce important protective genes, facilitate preconditioning, and minimize reperfusion injury—all in a variety of important organ systems.

However, most experimental demonstrations have involved single injury (*i.e.*, one hit such as sepsis or hypoxia or high stretch) scenarios, and this is a limitation, especially for studies of acute lung injury. In patients in intensive care unit (ICU) requiring mechanical ventilation for Acute Respiratory Distress Syndrome, the lungs have almost invariably suffered two "hits": the first is the initial reason for needing acute care (*e.g.*, sepsis, trauma); and the second is an inevitable degree of added injury resulting from mechanical ventilation.

The authors of the current study recognized this limitation and designed their studies accordingly.[2] They attempted to reproduce a clinical sequence consisting of sepsis followed by injurious ventilation, as is often associated with injured lungs in patients. They used inhaled endotoxin (lipopolysaccharide) to model pulmonary sepsis and subsequently applied high tidal volumes with a special mechanical ventilator to cause ventilator-induced lung injury—the experimental approach is beautifully illustrated in the article.

"… studying isoflurane and learning about its effects have opened our horizons (and minds) to alternative approaches for the prevention or treatment of pulmonary edema that complicates sepsis or mechanical ventilation."

The key experiments demonstrated that treatment with isoflurane in the interval between endotoxin exposure and mechanical ventilation resulted in less overall lung injury. Isoflurane preserved respiratory compliance; because histologic sections demonstrated similar levels of inflammatory cells but less interstitial edema, it seemed that the preserved lung function was due to lessened capillary leak rather than an antiinflammatory effect. This was then supported by direct measurement of capillary leak.

Of course the major factor responsible for protection against alveolar edema is the alveolar–capillary barrier, and so-called "tight junctions" are a key component of this barrier. Additional experiments used cultured epithelial cells to demonstrate that the combination of lipopolysaccharide (again, mimicking infection) and cell stretch (reflecting high tidal volume) resulted in the cells losing key proteins that are important to "tight junctions." In these preparations, isoflurane prevented such loss. Although appreciation of tight junctions is central to this study, appreciating them is also central to the clinician who is concerned about pulmonary edema.

So what are "tight junctions?" Tight junctions are specialized structures that connect adjacent epithelial cells and define the border between apical (airway facing) and basolateral (tissue facing) parts of the cell.[4] They have characteristic

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proteins that span the cell membranes (*e.g.*, occludins, claudins, and junctional adhesion molecules), and the structures provide a barrier that controls the diffusion of small ions and water-soluble molecules between the cells. This barrier is essential to prevent airspace flooding, and its integrity is related directly to the protein composition of tight junctions. In the current study, preservation of one of the tight junction proteins (termed zona occludens 1) by isoflurane appears to be how it protects in this injury.[2] Of course, future studies examining other components of the tight junction might help further understand the mechanism.

That the observed protection is not due to an antiinflammatory effect is very important. Although some anesthetics exert important antiinflammatory effects,[5] there is the potential for mixed impact. Potent antiinflammatory effect may be beneficial where excess inflammation is causing harm (*e.g.*, systemic or pulmonary inflammation that interferes with organ function) but can be harmful where a robust inflammatory response is required for bacterial clearance or for tissue healing. Thus, organ protection that is mediated by an inflammation-independent mechanism might constitute a flexible and useful approach.

Anesthesiologists working in the operating room are interested in how their management strategies or choice of drugs (*e.g.*, isoflurane) may impact on outcome. In this sense, we are in an age where anesthesiologists are learning about the "meta-anesthetic" effects of their interventions on broad groups of patients. Some phenomena are adverse and very concerning, such as postoperative cognitive dysfunction or neurodevelopmental delay in children, whereas others seem beneficial (*e.g.*, prevention of long-term pain or mitigation of tumor spread with regional anesthesia). Of course few of these issues are proven beyond doubt in patients, and while awaiting definitive answers, we must support and be alert to emerging high-quality research.

A narrower patient spectrum is made up of critically ill patients who need emergent surgery. Here the time spent in the operating room under the care of the anesthesiologist may represent a window in which there is either a risk of a critically ill patient acquiring additional injury (*e.g.*, excessive lung inflation or blood transfusion) or an opportunity to receive additional protection. The current study sheds light on the latter concern because if the current data are borne out, isoflurane—or perhaps other volatile agents—might become a preferred anesthetic where risk–benefit profile is favorable.

Many anesthesiologists are also responsible for the ongoing care of critically ill patients in the ICU. Thus, the current study may have additional relevance because in many parts of the world, volatile anesthetics (especially isoflurane) are a standard care for providing sedation to mechanically ventilated patients in the ICU. This approach affords precise titration to effect as well as the unique ability to remove the sedative from the patient as desired, in contrast to removal of intravenous sedatives that require metabolism by sufficiently functioning organ systems (or removal by dialysis). Thus, should the findings of the current study be replicated in patients, those in the ICU might especially benefit.

The simplest and most direct application of the current study might ultimately therefore be selective use of volatile agents in patients with the intent of protecting their lungs. Of course science usually takes a meandering course, and the major impact of studies such as this might not be the use of any particular anesthetic, but rather the insights gained by studying the agent. It might not be so important that anesthesiologists use volatile agents in the scenarios referred to above, but rather that studying isoflurane and learning about its effects have opened our horizons (and minds) to alternative approaches for the prevention or treatment of pulmonary edema that complicates sepsis or mechanical ventilation. It is here that research with mechanistic insight trumps research based only on observation; we might learn how to modulate tight junctions with other means and better help our patients with pulmonary edema.[6] It is for demonstrating new insights that we are most grateful to Englert *et al.* for their excellent contribution.

Competing Interests

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