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WHAT'S NEW IN INTENSIVE CARE

Lung protective properties of the volatile anesthetics

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Background

While intravenous and volatile anesthetics are both effective sedatives, providers may be able to take advantage of potential differences between their non-anesthetic properties when deciding the best regimen for their patient. For example, volatile agents may offer myocardial protection from ischemia–reperfusion injury, a theory supported by a recent meta-analysis showing that sevoflurane anesthesia for cardiac surgery was associated with significant reductions in postoperative troponin concentrations and superior postoperative cardiac function compared to total intravenous anesthesia [1]. Similar investigations have shown that volatile anesthetics also protect the central nervous, renal, and hepatic systems from inflammatory injury [2]. As the use of volatile agents gains popularity in the intensive care unit (ICU) setting, evidence suggesting that volatile anesthetics may also protect against inflammatory lung injury may provide insight into the potential additional benefit these agents can offer for the lung-injured patient.

Preclinical data

Volatile anesthetics have been shown in preclinical models to both prevent and minimize the extent of inflammatory lung injury. The most commonly proposed mechanism for these effects is through a reduction in pro-inflammatory cytokine release. For example, incubation of human airway epithelial cells with sevoflurane after anoxia reduces the mRNA expression of interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein 1a through an inhibition in the nuclear translocation of nuclear factor kappa beta (NFKb) [3]. Additional work using a rat model of acute respiratory distress syndrome (ARDS) showed that preconditioning with isoflurane prevents increases in inflammatory mediators found in bronchoalveolar lavage (BAL) samples and reduces histological evidence of lung injury via upregulation of reactive oxygen species in the pre-exposure period [4].

Arguably the mechanism of this effect could stem from a systemic reduction in inflammation also seen with intravenous anesthetics. However, Ferrando's work in a porcine model of ARDS showing that pre-exposure to sevoflurane results in reduced levels of BAL inflammatory markers and neutrophil counts compared to propofol suggests a local effect rather than a systemic one [5]. Recently, a novel pathway of lung protection for volatile anesthetics has been suggested. In a murine model mimicking a patient with ARDS who is then exposed to ventilator induced lung injury (VILI), Englert's group found that administration of volatile anesthetics during the mechanical ventilation phase reduced the degree of physiologic lung dysfunction not through reductions of inflammatory mediators but rather through preservation of alveolar-epithelial integrity [6]. A schematic representation summarizing the proposed mechanisms of lung protection is found in Fig. 1.

Human data

Although preclinical investigations have produced substantial evidence supporting the lung protective effects of volatile anesthetics, human data in this field is lacking. Therefore, intensivists looking for human correlates must rely on evidence largely from studies involving operative anesthetics. Data in patients undergoing thoracic surgery with one lung ventilation (OLV) suggests that patients given desflurane have significantly lower BAL markers of lung inflammation in the ventilated lung compared to patients anesthetized with propofol [7]. Reductions in the inflammatory markers in the operative (non-ventilated) lung can be less pronounced, supporting a local effect

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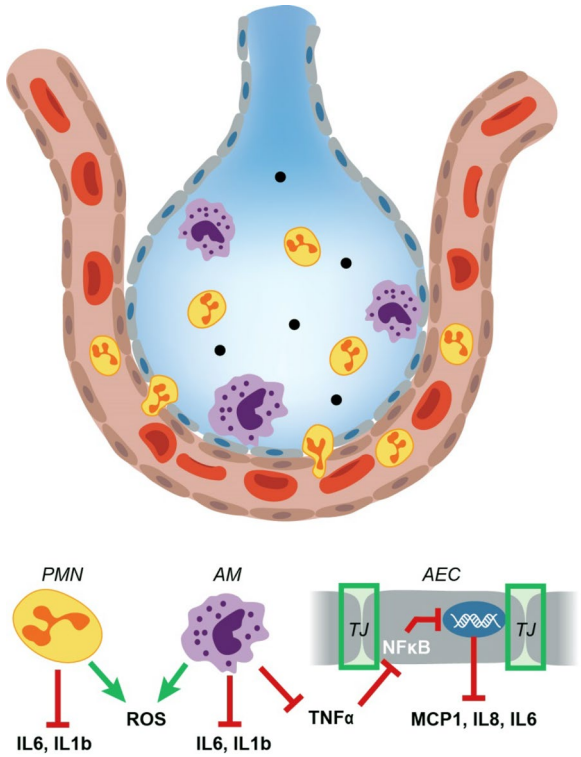

Fig. 1 Mechanisms of lung protection for the volatile anesthetics. Depicted is a representation of the alveolar capillary interface with the relevant cell types and mediators involved in lung injury. *Red arrows* indicate processes inhibited by volatile anesthetics, *green arrows* indicate processes enhanced by volatile anesthetics. The *green boxes* represent preservation of tight junctions. *PMN* polymorphonuclear cell, *AM* alveolar macrophage, *AEC* alveolar endothelial cell, *IL6* interleukin 6, *IL1b* interleukin 1 beta, *ROS* reactive oxygen species, *TNFa* tumor necrosis factor alpha, *TJ* tight junction, *NFKb* nuclear factor kappa beta, *MCP1* monocyte chemoattractant protein 1, *IL8* interleukin 8

on lung tissue [8]. Initial work searching for differences in clinical outcomes, not just inflammatory markers, suggested that the effect of the inhaled agents on oxygenation or hemodynamics during OLV were negligible as compared to patients receiving propofol [9]. However, De Conno later showed not only reduced lung inflammation in OLV patients anesthetized with sevoflurane compared to propofol, but also significant reductions in composite adverse events including pneumonia, atelectasis, pleural effusion, and bronchopleural fistula [10]. A similar reduction in pulmonary complications has been demonstrated in a recent meta-analysis showing that volatile as opposed to intravenous anesthesia is associated with a significant reduction in overall mortality for cardiac surgical patients [11]. Although specific prospective data regarding the use of inhaled sedation in the ICU to prevent or treat lung injury is lacking, retrospective analysis of patients receiving inhaled sedation suggests an association between its use and reductions in 1-year and in-hospital mortality, perhaps related to a significant increase in ventilator-free days compared to sedation with intravenous agents [12].

Comparative effects of different volatile agents

While substantial evidence points to a lung protective effect of the volatile agents as compared to propofol, limited data exists comparing how the various agents may differ with respect to this effect. Commonly thought to be an airway irritant in clinical practice, early data from porcine models showed that desflurane administration may result in elevated levels of biomarkers of lung oxidative stress when compared to propofol or sevoflurane [13]. Additionally, Strosing found that mice anesthetized with isoflurane and sevoflurane exhibited less evidence of inflammation in BAL fluid and histological samples, while mice given desflurane had similar levels of injury compared to controls [14]. To date, human studies directly comparing the lung protective properties of the different volatile anesthetics generally have not found similar results. In 2011, Schilling's group conducted a trial involving the comparative effect of sevoflurane, desflurane, or propofol on patients undergoing OLV and found that patients receiving either desflurane or sevoflurane experienced lower levels of inflammatory markers in BAL samples compared those receiving propofol, but a significant difference was not found between volatile groups [15]. Lastly, multiple forthcoming investigations regarding xenon anesthesia promise to clarify its potential role in limiting lung injury.

Summary

Use of inhaled anesthetics in the ICU is conceptually appealing as they offer a safe, effective, and easily titratable method of sedation. The possibility of an additional lung protective effect would make use of these drugs even more enticing. Volatile anesthetics have been shown to minimize existing lung injury as well as prevent new lung injury in various preclinical models of ARDS, but human data regarding this specific topic is lacking. Further research is necessary to clarify whether the findings from the laboratory and operating room are translatable to ICU patients suffering from or at risk for ARDS. If a correlation is found, investigators may then be able to provide additional insight into the potential superiority of one particular agent over another, dose effects, and application of the inhaled agents as preventative, therapeutic, or both. Answering these important clinical questions could one day lead to improved outcomes for lung-injured patients.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-016-4429-x) contains supplementary material, which is available to authorized users.

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References

1. Li F, Yuan Y (2015) Meta-analysis of the cardioprotective effect of sevoflurane versus propofol during cardiac surgery. BMC Anesthesiol 15:128
2. Lee YM, Song BC, Yeum KJ (2015) Impact of volatile anesthetics on oxidative stress and inflammation. Biomed Res Int 2015:242709
3. Watanabe K, Iwahara C, Nakayama H, Iwabuchi K, Matsukawa T, Yokoyama K, Yamaguchi K, Kamiyama Y, Inada E (2013) Sevoflurane suppresses tumour necrosis factor-alpha-induced inflammatory responses in small airway epithelial cells after anoxia/reoxygenation. Br J Anaesth 110:637–645
4. Chung IS, Kim JA, Kim JA, Choi HS, Lee JJ, Yang M, Ahn HJ, Lee SM (2013) Reactive oxygen species by isoflurane mediates inhibition of nuclear factor kappaB activation in lipopolysaccharide-induced acute inflammation of the lung. Anesth Analg 116:327–335
5. Ferrando C, Aguilar G, Piqueras L, Soro M, Moreno J, Belda FJ (2013) Sevoflurane, but not propofol, reduces the lung inflammatory response and improves oxygenation in an acute respiratory distress syndrome model: a randomised laboratory study. Eur J Anaesthesiol 30:455–463
6. Englert JA, Macias AA, Amador-Munoz D, Pinilla Vera M, Isabelle C, Guan J, Magaoay B, Suarez Velandia M, Coronata A, Lee A, Fredenburgh LE, Culley DJ, Crosby G, Baron RM (2015) Isoflurane ameliorates acute lung injury by preserving epithelial tight junction integrity. Anesthesiology 123:377–388
7. Schilling T, Kozian A, Kretzschmar M, Huth C, Welte T, Buhling F, Hedenstierna G, Hachenberg T (2007) Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. Br J Anaesth 99:368–375
8. Sugasawa Y, Yamaguchi K, Kumakura S, Murakami T, Suzuki K, Nagaoka I, Inada E (2012) Effects of sevoflurane and propofol on pulmonary inflammatory responses during lung resection. J Anesth 26:62–69
9. Beck DH, Doepfmer UR, Sinemus C, Bloch A, Schenk MR, Kox WJ (2001) Effects of sevoflurane and propofol on pulmonary shunt fraction during one-lung ventilation for thoracic surgery. Br J Anaesth 86:38–43
10. De Conno E, Steurer MP, Wittlinger M, Zalunardo MP, Weder W, Schneiter D, Schimmer RC, Klaghofer R, Neff TA, Schmid ER, Spahn DR, Z'Graggen BR, Urner M, Beck-Schimmer B (2009) Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology 110:1316–1326
11. Uhlig C, Bluth T, Schwarz K, Deckert S, Heinrich L, De Hert S, Landoni G, Serpa Neto A, Schultz MJ, Pelosi P, Schmitt J, Gama de Abreu M (2016) Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and meta-analysis. Anesthesiology 124:1230–1245
12. Bellgardt M, Bomberg H, Herzog-Niescery J, Dasch B, Vogelsang H, Weber TP, Steinfort C, Uhl W, Wagenpfeil S, Volk T, Meiser A (2016) Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients: retrospective analysis. Eur J Anaesthesiol 33:6–13
13. Allaouchiche B, Debon R, Goudable J, Chassard D, Duflo F (2001) Oxidative stress status during exposure to propofol, sevoflurane and desflurane. Anesth Analg 93:981–985
14. Strosing KM, Faller S, Gyllenram V, Engelstaedter H, Buerkle H, Spassov S, Hoetzel A (2016) Inhaled anesthetics exert different protective properties in a mouse model of ventilator-induced lung injury. Anesthesia Analg 123:143–151
15. Schilling T, Kozian A, Senturk M, Huth C, Reinhold A, Hedenstierna G, Hachenberg T (2011) Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. Anesthesiology 115:65–74