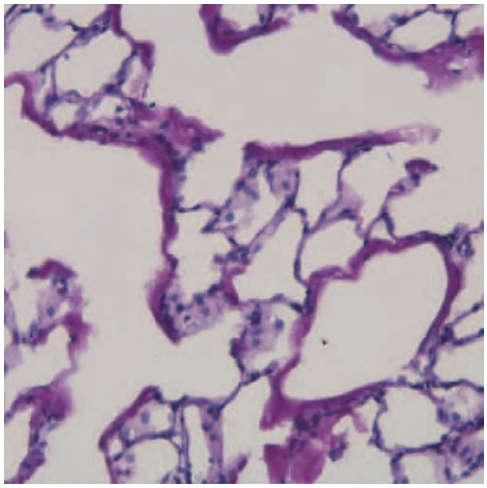
Should We Stop for Growth Arrest-specific 6 in Acute Respiratory Distress Syndrome?

Jae-Woo Lee, M.D., Hideya Kato, M.D.

LOW tidal volume mechanical ventilation is the primary supportive therapy for critically ill patients with acute respiratory distress syndrome. Surprisingly, despite widespread acknowledgment of its protective effects and implementation, overall mortality rates in acute respiratory distress syndrome have remained relatively unchanged.[1] Due to the patchy nature of the injury, a possible explanation may be a deleterious effect of even low tidal volume mechanical ventilation in acute respiratory distress syndrome, overdistention of "normal" aerated lung resulting in inflammation and dysfunction. During mechanical ventilation, the flow of gas into the lung takes the path of least resistance. Areas of the lung that are collapsed (atelectasis) or consolidated or filled with secretions as in acute respiratory distress syndrome will be underinflated, while those areas that are relatively normal will be overinflated, becoming overdistended and injured. Consequently, more research is needed to better understand the inflammatory injury within the "baby" lung during acute respiratory distress syndrome. Recently, growth arrest-specific 6 (Gas6), an endogenous agonist of an antiinflammatory receptor with known immunomodulatory properties, Axl, was found to be elevated in patients with sepsis, the leading cause of acute respiratory distress syndrome.[2] In this month's issue of Anesthesiology, Otulakowski *et al.* sought to determine whether high tidal volume mechanical ventilation in mice, a preclinical model of overdistension in acute respiratory distress syndrome, resulted in changes to known antiinflammatory receptor pathways such as Axl.[3]



"…[D]esensitization of anti-inflammatory pathways … may be involved in the inflammatory response seen in ventilator-induced lung injury."

Axl is a cell surface receptor in the Tyro3, Axl, and Mer tyrosine kinase family, which is involved with regulation of inflammation, efferocytosis, and apoptosis. In acute organ injury models, Tyro3, Axl, and Mer stimulation elicited potent immunosuppressive functions due to induction of regulatory factors such as suppressor of cytokine signaling 1, suppressor of cytokine signaling 3, and Twist, which inhibited both toll-like receptor- and cytokine-driven immune responses.[4] The relative importance of Axl signaling in acute respiratory distress syndrome was suggested by the finding that an endogenous agonist, Gas6, was elevated in patients with sepsis,[2] the leading cause of acute respiratory distress syndrome, and elevated Gas6 levels within 24 h of admission to the intensive care unit were predictive of intensive care unit mortality in patients with sepsis.[5]

In their study, Otulakowski *et al.*[3] explored the role of Axl signaling and the impact of Axl inhibition in an *in vivo* murine model of mild ventilator-induced lung injury induced by mechanical ventilation with 20 ml/kg tidal volume for 4 h. The authors originally hypothesized that inhibition of Axl would reduce expression of the antiinflammatory protein, suppressor of cytokine signaling 1-3, thus worsening lung injury during mechanical ventilation. However, surprisingly, Axl blockade with R428, a small molecule inhibitor, in mice with ventilator-induced lung injury was not associated with increased injury and had no additional effects on lung compliance, inflammation, permeability, or oxygenation compared to ventilator-induced lung injury mice despite blockade of the principal Axl downstream target, suppressor of cytokine signaling 3. In addition, the shedding of soluble Axl, which can sequester Gas6 and act as a decoy receptor, was increased with ventilator-induced lung injury but unchanged with R428 pretreatment; it remained unclear whether the level of soluble Axl with ventilator-induced lung injury completely sequestered Gas6, diminishing the capacity of R428 for further antagonism. To understand the mechanism, the authors injured isolated rat pulmonary microvascular endothelial cells with cyclic mechanical stretch *in vitro* and found that cyclic mechanical stretch desensitized Axl to the effects of exogenous Gas6 in part due to calcium influx *via* stretch-activated calcium channels. The desensitization of Axl was not due to increased soluble Axl release; inhibition of A disintegrin and metalloprotease 17, which was critical for soluble

Image: Ventilator-induced lung injury, from Izquierdo-García J: Anesthesiology 2014; 120:694–702.

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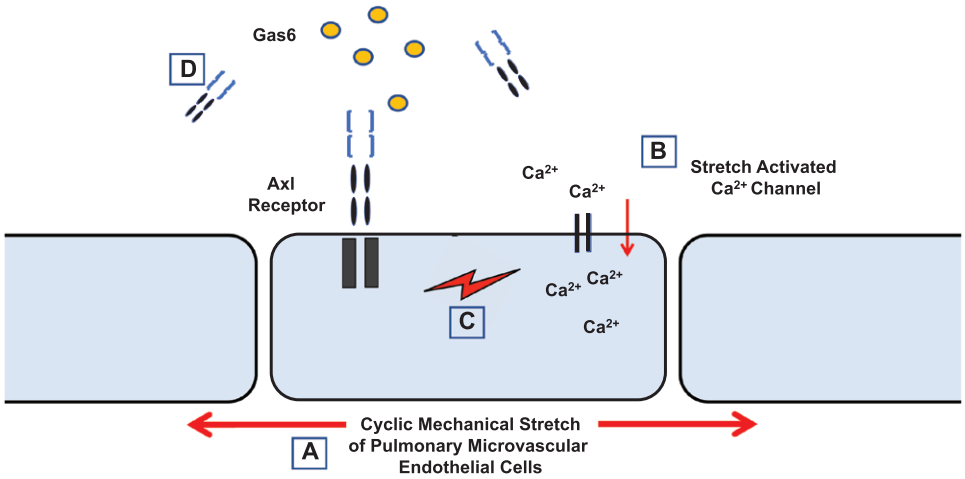

Fig. Role of Axl receptor in ventilator-induced lung injury. (*A*) Intrapulmonary cyclic mechanical stretch as seen in ventilator-induced lung injury may activate (*B*) calcium channels, leading to the influx of Ca^{2+}, which desensitizes (*C*) the Axl receptor to its agonist growth arrest-specific 6 (Gas6). The desensitization of the Axl receptor is not due to increased (*D*) soluble Axl release. The clinical implication is that inhibition of the stretch-activated Ca^{2+} channels may restore the immunosuppressive properties of Axl, dampening the inflammation seen in ventilator-induced lung injury.

Axl formation, did not protect endothelial cells from stretch-induced desensitization of Axl to its ligand, Gas6 (figure). Thus, the results suggested that high tidal volume mechanical ventilation or cyclic mechanical stretch may not only induce inflammation but also inhibit the lung's ability to diminish the injury by desensitizing antiinflammatory receptors such as Axl.

The clinical and translational implications of this study are severalfold: (1) More effort is needed to better understand the effect of low tidal volume mechanical ventilation in the aerated lungs from acute respiratory distress syndrome patients at a cellular and molecular level to limit its deleterious effects given that results to further reduce mortality in acute respiratory distress syndrome in randomized controlled trials have been mixed[6]; (2) in addition, these deleterious effect may not be entirely induced by inflammation from ventilator-induced lung injury, but, as suggested by this study, by desensitizing the lung's antiinflammatory pathways; (3) given the relative importance of Axl desensitization *in vitro* seen in endothelial cells and the elevated levels of Gas6 found in septic patients, targeting the stretch-activated ion channel in ventilator-induced lung injury may be a promising therapeutic approach; and (4) future research into the mechanisms underlying Axl desensitization at the cellular level may yield additional targets for the development of therapy for acute respiratory distress syndrome. With the advent of new technology such as time of flight mass cytometry, investigators are now capable of studying the entire signaling pathways of individual cells whether from a ventilator-induced lung injury rodent or from human acute respiratory distress syndrome lung tissue samples.

There are several limitations: (1) Although ventilator-induced lung injury may be a reasonable preclinical rodent model of overdistention of aerated lung in acute respiratory distress syndrome patients, it is unclear whether the deleterious effects are also seen in human acute respiratory distress syndrome lungs; are we observing ventilator-associated lung injury or ventilator-induced lung injury? (2) Because Axl receptors are also found in alveolar epithelial cells, which will receive the brunt of the cyclic mechanical stretch induced by high tidal volume mechanical ventilation, and in immune cells, such as macrophages, further studies are needed to determine whether the results *in vitro* with endothelial cells accurately depict what was seen *in vivo*.

In summary, Otulakowski *et al.* proposed a novel idea that desensitization of antiinflammatory pathways such as through Axl receptor may be involved in the inflammatory response seen in ventilator-induced lung injury. The implication of the results was that targeting the stretch-activated ion channel in ventilator-induced lung injury may be a promising therapeutic approach. However, perhaps more importantly, the study also highlighted the critical need to better understand the pathology that occurs in the aerated lungs in patients with acute respiratory distress syndrome during ventilation with low tidal volume given the limitation of the preclinical rodent models of ventilator-induced lung injury.[7]

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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.

Correspondence

Address correspondence to Dr. Lee: jae-woo.lee@ucsf.edu

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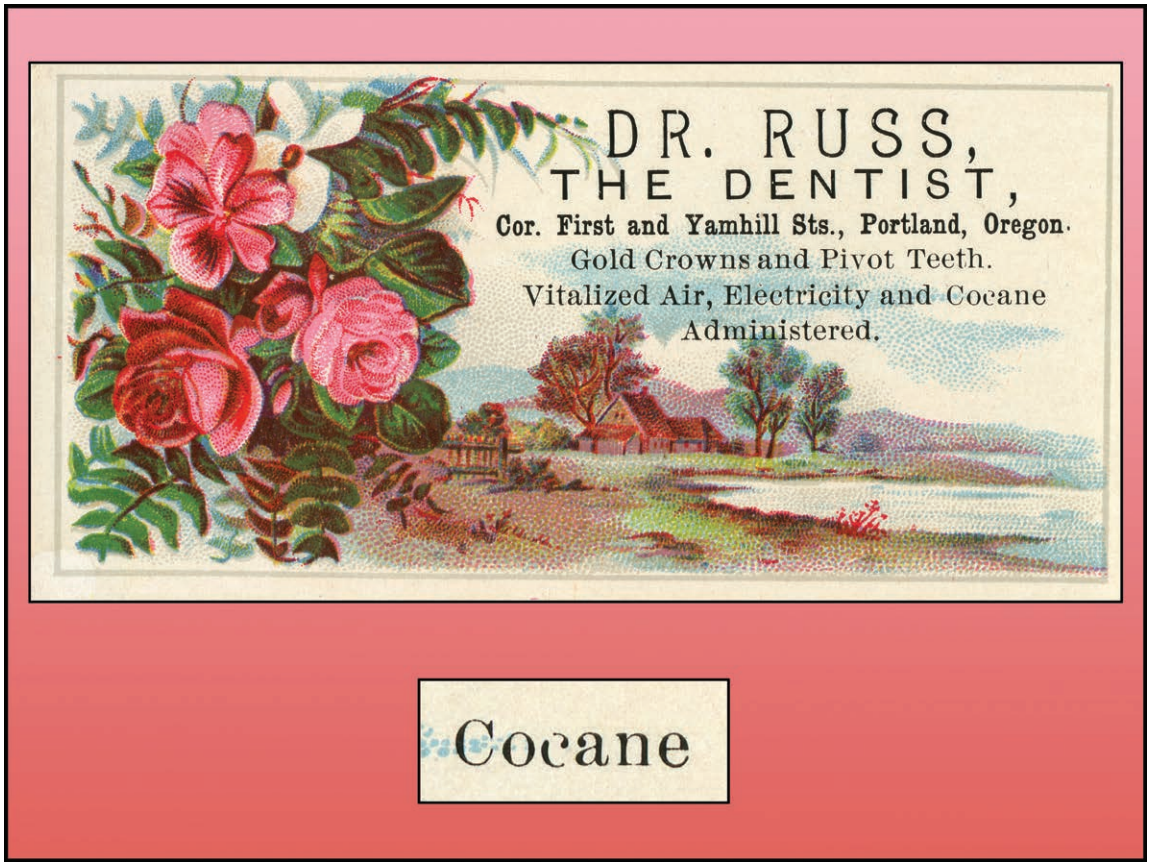

In Portland, Oregon in 1880, dentist Hiram M. Russ shared an office reception area with his wife, the town photographer. When he mistakenly plopped a well-dressed woman into his dental chair, she demanded that he unhand her, as she was there to be photographed by Mrs. Russ. Hapless Dr. Russ was ridiculed for this episode in the local press. As his dental practice expanded, he preferred to avoid the nausea and flammability associated with ether anesthetics. Indeed, by the 1890s, Dr. Russ had begun advertising his anesthetic use of "Vitalized Air, Electricity and Coca[i]ne" (*above*). In 1907, a second news story portrayed Dr. Russ in another explosive situation. This time, Dr. Russ suffered crippling injuries while pressurizing a vulcanizer around flammable office chemicals: "One hand was blown from his arm and one of his legs pierced by flying portions of steel." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.