reduce CVC and epidural errors seem like a good starting point.

Sir Liam Donaldson, the Chief Medical Officer of the United Kingdom and the Chair of the World Alliance for Patient Safety, has challenged health care by asking, "When will we be able to broadly reduce hazards?" Sir Donaldson uses the aviation industry's methods of handling safety hazards as a model for health care to follow. He presents an example of an imaginary "orange wire" on an airplane that is found to be frayed and is thought to be more likely a defect in the design of the wire rather than normal wear and tear. The aviation industry has a system whereby this orange wire would most likely be checked and repaired on every airplane of that model throughout the world in an expeditious fashion.[5] Hove *et al.* have taken the first step in identifying the "orange wires" we hope we will now work toward eliminating these risks.

Eugenie Heitmiller, M.D., Elizabeth Martinez, M.D., Peter J. Pronovost, M.D. Quality & Safety Research Group, Baltimore, Maryland, and Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital, Baltimore, Maryland. eheitmil@jhmi.edu

References

1. Cheney FW: The American Society of Anesthesiologists Closed Claims Project: What have we learned, how has it affected practice, and how will it affect practice in the future? ANESTHESIOLOGY 1999; 91:552–6

2. Hove LD, Steinmetz J, Christoffersen JK, Møller A, Nielsen J, Schmidt H: Analysis of deaths related to anesthesia in the period 1996–2004 from closed claims registered by the Danish Patient Insurance Association. ANESTHESIOLOGY 2007; 106:675–80

3. Studdert DM, Mello MM, Brennan TA: Medical malpractice. N Engl J Med 2004; 350:283–92

4. Lee LA, Domino KB: The Closed Claims Project: Has it influenced practice and outcome. Anesthesiol Clin North Am 2002; 20:485–501

5. Donaldson L: When will health care pass the orange-wire test? Lancet 2004; 364:1567–8

Anesthesiology 2007; 106:656–8

Imaging Inflammation in Acute Lung Injury

COMPUTED tomographic imaging provided key early insights into the pathophysiology of adult respiratory distress syndrome and acute lung injury, highlighting the heterogeneity of tissue involvement as a hallmark characteristic and demonstrating the effects of positive end-expiratory pressure (PEEP) and tidal volume on lung recruitment and regional overdistension.[1,2] These observations generated a rationale for management with PEEP and limited tidal volumes that has been refined and validated through years of basic and clinical studies. It is generally accepted that regional mechanical stresses due to "injurious" mechanical ventilation—primarily overdistension and cyclic airspace opening and closing—are associated with inflammatory processes that induce or exacerbate preexisting lung injury. However, the precise mechanisms by which this occurs or even which mechanical events are primarily responsible have not been defined. In this issue of ANESTHESIOLOGY, Musch *et al.*[3] present a sophisticated study that takes physiologic imaging to a new level, combining positron emission technology imaging of regional aeration, perfusion, gas exchange, and cellular metabolic activity (inflammation) to provide new insights into the pathogenesis of ventilator-associated or ventilator-induced lung injury.

This Editorial View accompanies the following article: Musch G, Venegas JG, Bellani G, Winkler T, Schroeder T, Petersen B, Harris RS, Vidal Melo MF: Regional gas exchange and cellular metabolic activity in ventilator-induced lung injury. ANESTHESIOLOGY 2007; 106:723–35.

Using a novel large animal model of ventilator-induced lung injury in which one lung was mechanically ventilated with overdistending end-inspiratory pressures while PEEP prevented cyclic end-expiratory airway opening and closing, these authors demonstrated increases in pulmonary uptake of the tracer fluoro-2-deoxy-D-glucose consistent with activation and extravascular migration of neutrophils. This regional inflammatory response occurred in only 90 min and before there was any detectible evidence of physiologic injury. In overdistended lungs also subjected to tidal opening and closing promoted by negative expiratory pressure, the inflammatory process was accelerated and accompanied by a familiar acute lung injury picture with volume loss and increased shunt. The contralateral control lung, held at constant pressure, remained unchanged. Although the authors are appropriately cautious about implicating overdistension as the crucial initiating mechanical event in injury development, this comprehensive approach, integrating *in vivo* regional physiology and mechanics with cellular responses, represents a major step toward a new paradigm for the study of ventilator-associated lung injury mechanisms relevant to clinical care.

Several aspects of this complex experimental model are notable. First and foremost is the use of a large animal model with human-scale, mechanical heterogeneity, and controllable hemodynamics, factors that greatly increase the translational potential of the findings.[4] The functional reserve of the lung normally masks the effect of significant local injury or dysfunction on global measures

Accepted for publication January 10, 2007. Supported by grant No. HL073994 from the National Institutes of Health, Bethesda, Maryland, and grant No. DAMD 17-02-1-0732 from the Department of Defense, Washington, D.C. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

of pulmonary function such as arterial blood gas tensions or mechanics, making the early disease process difficult to study. By using noninvasive imaging to measure regional lung function *in vivo*, subclinical injury can be detected and, in combination with physiologic and metabolic imaging, its consequences probed. As illustrated by their ability to detect metabolic activation in the PEEP-treated lungs before any measurable physiologic lung injury, these approaches provide a new window into the earliest events in ventilator-associated or ventilator-induced lung injury pathogenesis.

Other strengths of this study include the use of a unilateral, pure ventilator-induced lung injury model. The nonventilated control lung was not affected, suggesting that "spillover" systemic activation without mechanical ventilation was not enough to cause an inflammatory response in the lung. Whether noninjurious ventilation to the control lung would promote a response, however, remains unanswered. Experimental lung injury induced in previously normal lungs by mechanical ventilation alone has been extremely difficult to produce, requiring days of mechanical ventilation in large animals[5,6] or extremes of tidal excursions in rodents.[7] The absence of an intravenous or intrapulmonary agent to incite lung injury, such as bacterial endotoxin, HCl, or oleic acid, allows the focus to remain on the mechanical events. Finally, the ability to measure regional blood flow distribution and, particularly, identify active redistribution of blood flow presumably due to intact hypoxic pulmonary vasoconstriction is a unique and underemphasized strength of this technique. By measuring both regional aeration and blood flow changes, it is possible to identify local physiologic injury even in the setting of minimal or no effects on global shunt fraction.

Recognizing the difficulty of performing these complex studies, there remain nonetheless some important limitations. The "nonphysiologic" nature of the negative pressure used to induce cyclic opening and closing may not be clinically relevant, although many fundamental observations have been made in nonphysiologic experimental models such as isolated, unperfused mouse lungs.[8] The inclusion of additional study groups, particularly negative expiratory pressure without overdistension, would strengthen the implication that overdistension is the primary injurious mechanical event. There is the presumption that the increased fluoro-2-deoxy-D-glucose uptake is a precursor to injury and that acute lung injury would eventually develop in the lungs protected with PEEP. Finally, we do not know for certain the role of cells other than neutrophils in the imaged metabolic activation, although the increased fluoro-2-deoxy-D-glucose uptake in neutrophil-depleted animals implies that other cell types are also involved.

Imaging techniques continue to drive progress in the rational management of patients with acute lung injury, although most of these studies involve patients already severely injured,[9,10] and therefore, inferences about causality are speculative. Although there have been attempts to use computed tomographic imaging[11–13] and regional molecular[13] and histologic techniques[12] in animal models to explore regional differences in the injury process, these approaches require tissue sampling and the destruction of multiple animals at fixed or arbitrary time points. Circulating and bronchoalveolar lavage cytokine concentrations have become accepted as global biomarkers to determine whether a ventilation pattern is safe or injurious,[10,14] but perhaps positron emission technology imaged metabolic activation or other localized measures such as computed tomographic–guided regional bronchoalveolar lavage will provide more specific indications as to what about that ventilation pattern is problematic. The study by Musch *et al.* thus represents an important new direction for future studies of acute lung injury pathogenesis for a number of important reasons. First, the heterogeneity of lung involvement and the insensitivity of global measures of function call for the use of noninvasive imaging techniques to quantify regional lung pathophysiology. Second, mechanically and hemodynamically relevant large animal models provide translatable insights and evaluation of proposed therapies or management protocols. Third, we need to develop techniques to relate the heterogeneous regional mechanics of acute lung injury to changes at a cellular and molecular level in these models. Armed with these tools, we can then turn our attention from managing the aftermath and toward understanding and preventing the initiation of lung injury in at-risk patients on mechanical ventilation.

Brett A. Simon, M.D., Ph.D., Department of Anesthesiology and Critical Care Medicine and Department of Medicine, The Johns Hopkins University, Baltimore, Maryland. bsimon@jhmi.edu

References

1. Gattinoni L, Caironi P, Pelosi P, Goodman LR: What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001; 164:1701–11

2. Rouby JJ, Puybasset L, Nieszkowska A, Lu Q: Acute respiratory distress syndrome: Lessons from computed tomography of the whole lung. Crit Care Med 2003; 31:S285–95

3. Musch G, Venegas JG, Bellani G, Winkler T, Schroeder T, Petersen B, Harris RS, Vidal Melo MF: Regional gas exchange and cellular metabolic activity in ventilator-induced lung injury. ANESTHESIOLOGY 2007; 106:723–35

4. Bhattacharya J: Lung injury: Sphingosine-1-phosphate to the rescue. Am J Respir Crit Care Med 2004; 170:928–9

5. Tsuno K, Prato P, Kolobow T: Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 1990; 69:956–61

6. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M: Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation: An experimental study. Am Rev Respir Dis 1987; 135:312–5

7. Dreyfuss D, Soler P, Basset G, Saumon G: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988; 137:1159–64

8. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 1997; 99:944–52

9. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354:1775–86

10. Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Hermann P, Mascia L, Quintel M, Slutsky AS, Gattinoni L, Ranieri M: Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 2007; 175:160–6

11. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, Aletti G, Porro GA, Irace M, Carlesso E, Carboni N, Lazzerini M, Gattinoni L: Prone position delays the progression of ventilator-induced lung injury in rats: Does lung strain distribution play a role? Crit Care Med 2005; 33:361–7

12. Tsuchida S, Engelberts D, Peltekova V, Hopkins N, Frndova H, Babyn P, McKerlie C, Post M, McLoughlin P, Kavanagh BP: Atelectasis causes alveolar injury in nonatelectatic lung regions. Am J Respir Crit Care Med 2006; 174:279–89

13. Simon BA, Easley RB, Grigoryev DN, Ma SF, Ye SQ, Lavoie T, Tuder RM, Garcia JG: Microarray analysis of regional cellular responses to local mechanical stress in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2006; 291:L851–61

14. Stuber F, Wrigge H, Schroeder S, Wetegrove S, Zinserling J, Hoeft A, Putensen C: Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. Int. Care Med 2002; 28:834–41