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Can We Get There if We Don't Know Where We're Going?

JERRY Reves' 2006 Rovenstine lecture,[1] which is published in this issue of ANESTHESIOLOGY, accurately describes the diminutive research portfolio of American academic anesthesiology departments; among medical specialties, only family medicine garners fewer National Institutes of Health grant dollars per faculty member. His lecture identifies the "root causes" for low research productivity, including failure to attract research-oriented trainees, low research expectations of residents and faculty, inadequate research mentorship, and antiresearch financial incentives. Reves' plan to improve anesthesiology research calls for (1) scholarships to recruit M.D., Ph.D. students to anesthesiology residencies; (2) increased research time during anesthesiology residency[2]; (3) incorporation of a mandatory research year into all subspecialty fellowship programs[3]; (4) changes in academic compensation plans to reward research; and (5) abolition of the Medicare teaching rule for anesthesiology. This lecture is a cogent précis of many of the "systems problems" that obstruct research training in anesthesiology and should be required reading for every anesthesiologist.

Although the hard decisions and sacrifices required to implement these structural improvements are indisputably essential, would implementation of all of Dr. Reves' prescribed remedies be sufficient to reinvigorate anesthesiology research? We think not. Physicians are attracted to research careers because they dream that they will solve a major medical problem. These dreams motivate physician–scientists to forego financial rewards, to accept criticism and rejection, and to persist through grant funding crises. Physician–scientists are attracted to fields such as internal medicine, pediatrics, and neurology because they dream of curing cancer, asthma, or Alzheimer's disease. Ask an anesthesiologist what pressing clinical problems they need science to solve and you will get a panoply of tentative answers—or silence. Grant deficiency is not our specialty's problem; it is merely a symptom of our intellectual malaise and lack of mission.

Our specialty should be proud of our significant contributions to patient safety. However, it is premature and counterproductive to content ourselves with the fact that few patients experience intraoperative death due solely to anesthetic mishap; we need to take ownership of the substantial perioperative morbidity and mortality (1 death per 1,000 cases) that is the reality of modern American surgery. There are underrecognized problems in perioperative medicine that kill tens of thousands of Americans annually and incapacitate many more. Postoperative renal failure, systemic inflammatory response syndrome, and cognitive dysfunction provide a few examples of such public health problems. Before we can invigorate research, we must identify, publicize, and embrace the problems that need to be solved. Compelling and solvable problems will attract the best and brightest to our field.

Reves' data also demonstrate that half of the National Institutes of Health funding to academic anesthesiology departments resides in just 10 departments. These departments are comparable to other clinical specialties in National Institutes of Health dollar per faculty. Why have these departments been able to achieve success, while so many others are failing? These departments are nurturing trainees and young faculty with resources, space, and encouragement and are not directing all of their income to faculty compensation. The result is that they develop faculty members who identify and begin to solve important clinical problems. With just a few such faculty members, critical mass is achieved, generating a local climate of intellectual excitement that attracts students and residents into starting research careers. A detailed analysis of common practices contributing to the research success of the "top 10" departments could provide a useful template that other departments could emulate.

Why do the majority of departments fail to achieve this critical mass? Debra Culley *et al.*[4] suggest in this issue of the Journal that inadequate academic leadership may be responsible for this poor performance. They show that anesthesiology chairpersons have a lesser history of grant funding and shorter publication records than do their surgical counterparts and that poor chairperson research credentials correlate with poor departmental research performance. Although the meager research credentials of most anesthesiology chairs may be due to an inadequate talent pool, it more likely reflects the values of those who select anesthesiology chairs; they

◆ This Editorial View accompanies the following two articles: Reves JG: We are what we make: Transforming research in anesthesiology. The 45th Rovenstine Lecture. ANESTHESIOLOGY 2007; 106:826–35; Culley DJ, Crosby G, Xie Z, Vacanti CA, Kitz RJ, Zapol WM: Career National Institutes of Health funding and scholarship of chairpersons of academic departments of anesthesiology and surgery. ANESTHESIOLOGY 2007; 106:836–42.

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apparently value the managerial skills of anesthesiology leaders more than their research skills.[5] The deans, surgeons, and hospital executives who sit on anesthesiology chair search committees are not convinced that there are compelling clinical problems in anesthesiology that necessitate a serious research effort. Although we would concede that a chairperson without strong research credentials may have the leadership skills and vision to build a strong research program, chairs that lack investigative credentials comparable to their counterparts in other departments are unlikely to compete effectively in securing the institutional resources (space, equipment, capital) required to initiate and sustain a research effort. Hence, the selection of a chair with weak academic credentials is less an indictment of the chair than a symptom of institutional conceptions and priorities around the role our specialty should play in the academic medical center.

How then will we succeed? The plan proposed by Reves is meritorious and should be endorsed and implemented. Removing obstacles to anesthesiology research and creating inducements can only have long-term benefit. However, it is important to realize these system changes are enabling but not sufficient; merely changing training rules will not rescue anesthesiology research. Our academic and political leadership needs to stop celebrating the fact that we do not actively harm patients and set their sites on a vision for dramatically improving perioperative outcomes. Even with the proposed systems changes and a new vision, improvement will only come from individual leaders and individual departments. These changes in mission, commitment, and organization should serve to stabilize the number of academic institutions that value and support anesthesiology research and hopefully make their efforts more robust. Implementation of the proposed changes is not likely to help the research efforts of the many anesthesiology departments that lack institutional commitment to anesthesia research and have selected leaders without the background to develop research programs. It is hoped that, in the long term, we can persuade some of these institutions of the imperative of research in our specialty.

We conclude by reiterating: Tactics are necessary for success, but only in support of a defined mission. If we can figure out where we are going, the plan proposed by Reves may just let us get there.

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Every Breath You Take, We'll Be Watching You

MASS spectrometry has enjoyed a prominent place in anesthesiology and critical care, enabling the routine monitoring of anesthetic gases, facilitating our understanding of volatile anesthetic pharmacokinetics and pharmacodynamics, and contributing immeasurably to routine patient care.[1–3] Although it is no longer used today for ordinary intraoperative gas monitoring, the legacy of mass spectrometry is the routine quantification of inspired and end-tidal anesthetic and respiratory gas concentrations, albeit by the now more ubiquitous infrared technology.

Shortly after the clinical introduction of propofol (2,6-diisopropylphenol in a lipid emulsion), I purchased a bottle of 2,6-diisopropylphenol from a chemical supply company for resident teaching. The aroma noticeable immediately upon opening the bottle suggested a sufficiently high vapor pressure to portend pulmonary propofol elimination, and hence the possibility of detecting and quantifying propofol in expired gas by the mass spectrometer then in use in the operating room. A proposal to our operating room's mass spectrometer manufacturer to investigate this possibility was not reviewed favorably, and the idea was soon forgotten.

Harrison *et al.*,[4] in a seminal investigation, gave proof of concept reality to the conjecture of pulmonary propo-

This Editorial View accompanies the following two articles: Takita A, Masui K, Kazama T: On-line monitoring of end-tidal propofol concentration in anesthetized patients. ANESTHESIOLOGY 2007; 106:659–64; Hornuss C, Praun S, Villinger J, Dornauer A, Moehnle P, Dolch M, Weninger E, Chouker A, Feil C, Briegel J, Thiel M, Schelling G: Real-time monitoring of propofol in expired air in humans undergoing total intravenous anesthesia. ANESTHESIOLOGY 2007; 106:665–74.

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fol elimination and its measurement. They applied a novel technology, proton transfer reaction mass spectrometry, to demonstrate propofol exhalation and its measurement, albeit without absolute quantification. They also demonstrated the feasibility of real-time measurement of propofol and its metabolites in expired breath. They suggested the possibility of defining an alveolar propofol concentration that connotes adequate anesthesia.

In this issue of ANESTHESIOLOGY are two investigations reporting further evaluation of real-time on-line pulmonary propofol monitoring.[5,6] Takita *et al.*[5] administered a propofol infusion and used a proton transfer reaction mass spectrometer to measure absolute propofol concentrations in exhaled gas. These were proportional to propofol blood concentrations in blood simultaneously obtained and measured by conventional techniques. After a propofol bolus, exhaled propofol concentrations rose and fell, expectedly. Hornuss *et al.*[6] used a different but related (both instruments use "soft ionization" techniques) ion–molecule reaction mass spectrometer to also measure, but not absolutely quantify, exhaled propofol. They also measured contemporaneously obtained blood propofol concentrations, and those in the gas phase after a blood sample was placed in a sealed vial. Within a patient, there were correlations between blood propofol concentrations and those in both expired gas and the gas above the blood in the vial. These investigations validate the proof of concept in several patients, and extend it by providing absolute quantification.

While intriguing, both reports leave open questions and limitations to the methods described, presenting challenges for technology refinement. Neither propofol instrument could measure carbon dioxide concentration; hence end-expiration could not be defined. To accomplish this, Takita *et al.* measured expired gas temperature, and Hornuss *et al.* used a second mass spectrometer to measure carbon dioxide, so the propofol measurements were "approximately" end-tidal. The proton transfer method required the averaging of 50 breath samples, over 5 min, because of measurement variability. In addition, inspired propofol concentrations were not zero. Although plasma concentrations peak within a few seconds after an intravenous propofol bolus, expired propofol concentrations did not peak for 5 min. Whether this reflects a delay in blood–gas transfer, pulmonary sequestration, or some other factor remains to be determined. Although ion–molecule reaction mass spectrometry found correlations between blood and gas propofol concentrations for any given patient, the slope of this relationship, and that between expired propofol content and that in the gas above the blood in a vial, were highly variable between patients. This might affect robust quantification and requires further evaluation and refinement. Nonetheless, these challenges do not affect the proof of concept.

Other unknown factors may affect propofol exhalation and quantification. What is the influence of the lipids in propofol formulations, or other factors, on the relationship between blood and expired 2,6-diisopropylphenol concentrations? Lipids can alter drug disposition. The presence of lipid in an emulsion of halothane delivered intravenously significantly decreased end-tidal halothane concentrations at blood halothane concentrations identical to those after inhalation.[7] Similarly, lipid content in blood markedly altered the isoflurane blood:gas partition coefficient and altered isoflurane elimination from blood to the lungs.[8] For propofol, there was a significant influence of lipid and formulation on pharmacodynamics and pharmacokinetics in anesthetized patients, most notably affecting the volume of distribution,[9] which might also affect pulmonary elimination. Blood lipid concentrations increase over time with propofol infusions. Not only may exogenous lipids affect propofol, but also endogenous lipids, because propofol is highly bound to serum lipids and proteins, and changes in cholesterol, triglyceride, and lipoprotein concentrations in blood affected the free concentration of 2,6-diisopropylphenol.[10] Other endogenous factors, such as pulmonary transfer from blood to alveolar gas, may also affect pulmonary propofol monitoring. Grossherr *et al.*[11] reported a 10-fold difference, between goats and pigs, in expired propofol concentrations at similar plasma concentrations. Whether endogenous or exogenous lipids, pulmonary factors, interindividual variability, or other factors affect either the pulmonary elimination of propofol or its measurement remains to be determined.

In the two reports in this issue of ANESTHESIOLOGY, exhaled 2,6-diisopropylphenol concentrations were extremely low, typically 2–5 parts per billion (ppb).[5] This has (at least) two implications. First, it demonstrates the exquisite sensitivity of the new mass spectrometry techniques. Although Takita *et al.* did not report their limits of quantification, their calibration curve ranged from 0.4 to 400 ppb. By comparison, exhaled volatile anesthetic concentrations are typically (at maintenance) 1–9% (10–90 *million* ppb), and an infrared anesthesia monitor with a detection limit of 0.1% has a sensitivity of 1 million ppb. Therefore, the proton transfer reaction mass spectrometer used by Takita *et al.* is approximately 10 million times more sensitive than conventional infrared anesthesia monitors. This is impressive. Second, elimination in exhaled alveolar gas is not likely to be a quantitatively significant route of the well-described extrahepatic elimination of propofol, in agreement with conclusions reached by measuring central venous and arterial propofol concentrations.[12,13]

A robust and reliable method to quantify blood 2,6-diisopropylphenol concentrations could have application in research and/or therapeutics. It could have broad applicability in assessing propofol pharmacokinetics. It could replace the frequent use of *predicted* plasma propofol concentrations as an *independent* variable in many clinical investigations. It could provide more accu-

rate achievement of desired propofol concentrations than those attained by target-controlled infusions based on population pharmacokinetic parameters. Pulmonary propofol concentrations could be used as a control variable for closed-loop anesthesia.[14,15] Whether this would provide a better result (however defined) than electroencephalogram-derived parameters or nociception as the control variable remains to be determined.

The addition of high-sensitivity mass spectrometry for alveolar propofol measurement is an enabling technology, which adds to our armamentarium of medical gas monitoring. With every breath you take, we'll be watching you.*

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* With homage to the musical group The Police.

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Identifying and Learning from Mistakes

THE American Society of Anesthesiologists has been lauded for the 1984 institution of its Closed Claims Project to identify patient safety hazards.[1] Although the time delay from identifying to mitigating a risk using closed claims is long, such claims are a vital source of data to improve patient safety. Hove *et al.*[2] built upon this rich history by reviewing 24 anesthesia-related death claims filed with the Danish Patient Insurance Association from 1996 to 2004.

In reviewing this article, it is important to consider the type of information available in claims data. Liability claims data do not provide valid rates of complications or deaths from anesthesia. Studies in the United States demonstrate that only a minority, approximately one in seven people, who are harmed by mistakes will submit claims, and many who have bad outcomes without an error also submit claims.[3] As such, using liability claims to estimate the incidence rate of harm is likely inaccurate.

Nevertheless, these data do provide us a rich opportunity to review a sample, albeit skewed, of anesthesia-related deaths and devise strategies to reduce the risk of recurrence. We wish the authors had gone further with this investigation. In reviewing the list of events in this study, it was noteworthy that 5 of the 24 deaths (21%) were classified as airway events, although only one resulted from failure to intubate or ventilate a difficult airway case. This low frequency is in contrast to the higher percentage of difficult airway–related deaths reported by the American Society of Anesthesiologists Closed Claims in the 1990s.[4] This could be sampling error, or may, in fact, represent the tremendous efforts by anesthesia professional societies to develop guide-

This Editorial View accompanies the following article: 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.

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lines for management of difficult airways and prevention of aspiration and for training programs to ensure that residents are competent in airway management. However, we have not applied this degree of focus in other areas.

An area ripe for improvement is the process of inserting central venous catheters (CVCs). Two of the four deaths related to CVC insertion in Hove's study were likely due to placement of a large-bore catheter into the carotid artery. Such events can be prevented with focused efforts to reduce the risk of a carotid puncture by using ultrasound guidance, and to confirm venous access with a small catheter before placement of a large catheter. The small catheter can be attached to a transducer or a fluid-filled column to show evidence of a venous pressure tracing, or absence of pulsatile flow and confirm that the catheter is in a vein. If the transducer shows an arterial waveform or the fluid-filled column does not drop when held above the level of the heart, the catheter should be removed. The extra few minutes spent performing this check could prevent a potentially devastating or even lethal complication.

Knowledge of appropriate CVC insertion will likely not result in broad improvements in patient safety until all members of the healthcare team realize that reducing risk of harm is of paramount importance and a system is established to teach this to trainees from the start. We recently learned how far we are from such a system. After investigating a fatal event involving the removal of a CVC, we identified wide variability in how residents were trained, supervised, and deemed competent to place or remove these lines. Indeed, many residents stated they were told contradictory statements such as "never do that" by one supervisor and "always do that" by another. For insertion and removal of CVC and many other procedures, we have not adhered to safety 101: Standardize your work processes, create independent checks for key steps, and learn from your mistakes. Our current training for most procedures is still based on "see one, do one, teach one."

An improved system would be based on knowledge, skills, and behaviors. A system to eliminate CVC-related errors could include

- developing an international guideline, training video, and knowledge test for CVC placement;
- creating a simulation program and developing a tool to evaluate competency for CVC placement; and
- developing a tool to evaluate performance in the real world.

Such evaluation tools should address not only the technical work but also the teamwork involved in placing these catheters. Although these types of programs are likely beyond the resources of most single institutions, it is possible within our professional communities. Professional societies can take a lead in developing such programs.

Another preventable error illustrated by this closed claims study was the erroneous attachment of an epidural catheter to an intravenous infusion that resulted in one death. Perhaps the most trumpeted improvement in anesthesia patient safety was nearly eliminating the ability to attach nitrous oxide tanks or hoses to oxygen connectors. This was accomplished by changing the shape of the yokes; the two physically cannot be connected as long as the fittings are not altered or broken. Despite the recognition this intervention received, other examples of eliminating or preventing mistakes are exceedingly rare. After the oxygen–nitrous oxide example, we should make different size connections for epidural and intravenous tubing devices so they physically cannot fit together. Such a change will require the concerted effort of many stakeholders. In the interim, hospitals could institute a policy to make this type of mistake visible. For example, we implemented a policy requiring that all epidural catheters and epidural infusion tubing be labeled with a bright-colored sticker stating "epidural only." Although this is less foolproof than changing the tubing connectors, the increased visibility could prevent harm.

There were three deaths that involved patients who had combined epidural and general anesthesia. This is concerning, although perhaps not surprising. When using a combined anesthetic technique and assuming that the risks from regional and general anesthesia are independent, basic probability informs us that experiencing a complication from either one is the sum of the probabilities of each technique. As such, patients who receive a combined technique may have a complication rate equal to the combined rates of regional and general anesthesia. For example, the risk of an intravascular infusion of bupivacaine is independent of the risk of the inability to intubate the trachea of the patient.

When we expose patients to the risk of two anesthetic techniques, there should be some benefit to offset that risk. Are the potential benefits of a combined technique, such as better pain control, sufficient to offset the increased risk of permanent or life-threatening neurologic injury? Who makes this decision? Are patients truly informed of this increased risk with combined techniques? While this requires further research and discussion, anesthesiologists should do their best to discuss the potential risks and benefits with patients to help ensure that they are making an informed decision.

The greatest value from the study by Hove *et al.* is identifying specific hazards and helping to prioritize where to focus patient safety improvement efforts. Our patients may be better served by learning deeply from a small number of hazards than learning superficially from a large number. We need to start diving deeper in our efforts to mitigate hazards. Efforts to

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.

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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.

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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

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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.

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