a group enriched for "faster" decliners as required for some clinical studies, its addition to already known markers is minimal (although again statistically significant, reflecting the large number of patients studied), and the decline in an individual identified in such a way can range from none to 250 ml/yr. The relative weakness of the relationships probably (at least in part) explains the lack of an association between CC16 and subsequent mortality.

The associated animal knockout studies add credence to this (even though in mice) with no influence of CC16 or its lack on lung morphology after smoke exposure. Clearly the number of mice required to detect an impact as little as that based on the human studies would be prohibitive and not worth the effort.

So despite a sound hypothesis and comprehensive human and relevant animal experiments, the CC16 data are disappointing and yet provide a highly important lesson to researchers. It remains possible that CC16 still has a role as a biomarker in some subset of patients with COPD, although this will require a prospective study with state-of-the-art phenotyping together with an understanding of what a measure of CC16 in the blood means. Does it reflect a pathophysiological process specific to COPD or is it just a byproduct of tissue/cell damage as seen in more general lung injury (6)? Does the degree of general pulmonary inflammation alone influence its detection and quantification in the blood due to degree of "back leakage" even if the damage is low? In reality, these questions would need resolving, but the study of CC16 alone would not be a reason for initiating a prospective study, although with sufficient understanding of what a measurement is telling us, CC16 could be included as part of a prospective panel of markers in highly phenotyped patients.

Big cohorts with long-term follow-up provide greater power for biomarker validation, although a "very weak" but "highly significant" relationship such as that described in the current issue provides little support for CC16 as a biomarker to understand the pathophysiology of the COPD syndrome or to be used to identify rapid decliners for interventional studies. Nevertheless, the data provide a vital lesson in interpretation for researchers.

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Robert A. Stockley, M.D., D.Sc.
Lung Function and Sleep Department
Queen Elizabeth Hospital Birmingham
Edgbaston, Birmingham, United Kingdom

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Volutrauma and Regional Ventilation Revisited

In 1992, Dreyfuss and Saumon coined the term "volutrauma" to emphasize that the choice of tidal volume is the single most important risk factor of mechanical ventilation–associated lung injury (1). In doing so, Dreyfuss and Saumon underscored that tidal volume is a better measure of lung parenchymal stress than airway pressure because the latter is often dominated by the elastic properties of the chest wall (2). It is now well established that mechanical ventilation with large tidal volumes can damage the lung by distinct biophysical injury mechanisms (3). These include tensile stress associated with so-called alveolar overstretch, interfacial stress associated with surfactant dysfunction, accumulation of liquid and foam in airspaces, cyclic recruitment and derecruitment of unstable lung units, and shear stress between interdependent units with different mechanical properties. Although research on biophysical lung injury mechanisms is clearly motivated by concerns for complications of positive pressure ventilation, one may reasonably ask if the same mechanisms would not operate in spontaneously breathing patients as well. In other words, assuming similar tidal volumes, is the topographical distribution of parenchymal stress fundamentally different between the modes of breathing? This question has occupied respiratory physiologists during the latter half of the 20th century and has now reemerged in a clinical context in the article by Yoshida and colleagues (pp. 1420–1427) in this issue of the *Journal* (4).

Yoshida and colleagues compared the vertical distributions of inspired gas between assisted and controlled mechanical ventilation in a patient using electrical impedance tomography (EIT). To their surprise, they observed a significant translocation of alveolar gas from nondependent to dependent regions of diaphragm-apposed lung during the patient's assisted positive pressure breathing. They characterized the phenomenon as pendelluft (derived from the German words for pendulum and air), noted its absence during paralysis and controlled mechanical ventilation, and hypothesized that it was caused by a nonuniform change in lung surface pressure (pleural pressure) during diaphragm contraction. This interpretation is qualitatively consistent with prior observations in normal recumbent anesthetized humans, in whom muscle paralysis and mechanical ventilation was shown to be associated with a different ventilation distribution than spontaneous breathing (5). These changes in regional ventilation were attributed to different deformations of the chest wall and different motion of the diaphragm between the modes of breathing (6).

Under normal circumstances, that is, in individuals with normal lungs and respiratory drive, these differences are modest at best, because the shear modulus of normal lungs (their resistance to an isovolumic shape change) approaches that of liquids (7),

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because mode-related differences in thoracic cavity shape are relatively small and because the sliding motions of lung lobes minimize parenchymal distortions (8). In comparison, the changes in regional ventilation and hence in parenchymal stress and strain in patients and animals with injured lungs as reported by Yoshida and colleagues were huge and are therefore of potential clinical and biologic significance (4).

To validate the patient findings and explore responsible mechanisms, Yoshida and colleagues measured the effects of breathing modality on regional volumes and pressures (parenchymal stress) in a porcine model subjected to lung injury by saline lavage. Topographical volume and ventilation distributions were inferred from density maps of EIT and high-speed computer tomography–derived images. Not only did these experiments confirm the presence of "occult" pendelluft during spontaneous pressure assisted breathing, but, more importantly, they revealed a very large effect size. For example, to achieve comparable tidal inflations of diaphragm-apposed dependent lung regions, the airway pressure amplitude of spontaneously breathing animals had to be increased from 10 cm H_2O to 28 cm H_2O after neuromuscular blockade. This resulted in a corresponding increase in global tidal volumes from 6 to 15 ml/kg. On that basis, Yoshida and colleagues conclude that spontaneous breathing in mechanically ventilated patients can cause unsuspected, transient overstretching of dependent lung regions with concurrent deflation of nondependent lung.

Notwithstanding the need to confirm these observations in different lung injury models and clinical settings, the pendelluft hypothesis challenges some firmly held beliefs. For example, proponents of assisted pressure release ventilation have long argued that the maintenance of diaphragm activity preserves the aeration of dependent lung and thereby leads to superior patient outcomes (9). Although clinical benefit of assisted pressure release ventilation remains to be established (10), Yoshida and colleagues' observations suggest that the prevention of dependent lung atelectasis by virtue of cyclic diaphragm contractions could come at considerable long-term cost. In fact, proponents of early neuromuscular blockade for patients with the adult respiratory distress syndrome (ARDS) will likely embrace the pendelluft hypothesis as one mechanistic explanation of the survival benefit associated with this intervention (11).

The proposed mechanism of overstretch injury requires that dependent diaphragm near lung regions remain recruitable at the prevailing local inflation pressures. This was clearly the case in lavage-injured pigs, but may not be the case in patients with established ARDS (12). Moreover, the presence of pleural fluid could serve to dissipate the heterogeneity in lung surface pressure, which drives the pendelluft phenomenon. It should be noted that Yoshida and colleagues' examples of "occult" pendelluft were generally observed under conditions of increased respiratory drive. This tends to magnify muscular chest wall distortions and may have biased the size of the pendelluft estimate. Aside from the postulated effect of lavage injury on the shear modulus and hence deformability of the lungs, the much lower respiratory drive of anesthetized uninjured pigs probably explains why pendelluft was not seen in animals with healthy lungs. In fact, inspiratory efforts against an occluded airway of a magnitude comparable to that reported in injured pigs had previously been shown to produce pendelluft between apical and caudal lobes in normal dogs (13). Finally, neither EIT nor computer tomography provides accurate information on the locations of distinct anatomic lung regions in time. As a result, it is not possible to assess the effects of diaphragm motion on rigid body displacement and rotation of a lobe or lung region. This could lead to the erroneous impression of recruitment as a neighboring region fills the space vacated by consolidated lung.

Notwithstanding these minor caveats, Yoshida and colleagues' observations are important. They emphasize that patients who breathe with seemingly lung-protective tidal volumes could still suffer biophysical lung trauma unless their respiratory drive and diaphragm motor output are carefully manipulated. If refined and confirmed, the pendelluft hypothesis has serious implications for the use of noninvasive mechanical ventilation in patients with impending or established ARDS. Mask ventilation imposes limits on the use of sedatives and narcotics, so its prolonged use may inappropriately delay intubation and lung-protective support (14). It took decades before the critical care community accepted low tidal volume mechanical ventilation as the standard of care. Yoshida and colleagues may have just added another important "wrinkle" to this story.

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Rolf D. Hubmayr, M.D.
Pulmonary and Critical Care Medicine
Mayo Clinic
Rochester, Minnesota

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