

present study from Alladina and colleagues is another important piece in this field. ■

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## Smoothing the Edges of Lung Protection

Two deceptively simple tools for improving the gas exchange and mechanics of patients with the acute respiratory distress syndrome (ARDS)—positive end-expiratory pressure (PEEP) and prone positioning—were brought to clinical attention nearly 50 years ago (1). Although the potential was soon recognized for PEEP to

simultaneously influence global lung mechanics, gas exchange, and hemodynamics (2), our understanding of its regional actions in ARDS and its relationship to body position has been slow to evolve. The early and elegant physiologic investigation of Suter and colleagues demonstrated that the PEEP associated with best tidal compliance during volume-controlled ventilation (lowest driving pressure) held simultaneous benefits for gas exchange efficiency and oxygen delivery. At the time, lung protection against ventilator-induced lung injury was not a recognized priority, and by today's standards, a large  $V_T$  was in use. It is interesting to note that the compliance-defined optimal value of PEEP was first shown in that early era (3) to be a function of the  $V_T$  delivered, a relationship that has been more recently confirmed (4). In today's routine practice, the effects of PEEP on the lung

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continue to be monitored by single “lumped parameter” variables (pressure and  $V_T$ ) measured at the airway opening.

Although improved oxygenation remains a key motivator for using PEEP, adjustments are now more often made with a careful eye toward finding a balance between the higher PEEP values needed to minimize tidal recruitment in the injured lung and the lower PEEPs need to avoid overdistension of a less injured lung. Finding the best trade-off between maintaining recruitment and avoiding overdistension has proven to be a challenge in the mechanically heterogeneous environment of ARDS. The injured lung is characterized by an increase in the normal vertical gradient of pleural pressure, primarily because of the superimposed weight of a heavy lung and mediastinum. The supine gradient of end-expiratory transpulmonary pressure ( $P_{tp}$ ) is thereby increased (5), declining from ventral to dorsal regions. Any increment of applied airway pressure, such as PEEP, tends to disproportionately expand the more compliant nondependent alveolar units.

Prone positioning, a method that usually (but not invariably) improves oxygenation even when PEEP falters, has taken somewhat longer to gain acceptance into clinical practice. Anatomically, dorsal portions of the chest wall are less compliant than the ventral portions, a disparity that is partially offset in the prone position by the buttressing of the ventral surface. These functional changes in the geographical distribution of  $P_{tp}$  tend to improve the uniformity of lung expansion. Importantly, in the prone position, the weight of the heart and mediastinal contents is relieved from the dorsal lung (6). The net effect is a more homogenous distribution of ventilation and  $P_{tp}$  (7) in the prone position.

In this issue of the *Journal*, Katira and colleagues (pp. 1266–1274) demonstrate experimentally in a porcine lung injury model (using electrical impedance tomography imaging and direct pleural pressure measurements by catheters placed in gravitationally dependent and nondependent zones) that diverse local actions of PEEP regarding lung unit distention are made more uniform by prone positioning (8). Consequently, a single value of PEEP applied to the airway opening in the prone position may exert similar distending forces on both dependent and nondependent lung units. These results help advance our mechanistic understanding of the PEEP–proning interaction. Although this is not the first study to indicate the homogenizing effect of prone positioning on PEEP-associated  $P_{tp}$ , it holds clear implications for clinical practice. Interestingly, while the regional splay of  $P_{tp}$  was narrowed by proning, the average  $P_{tp}$  was similar in both supine and prone positions. These latter experimental findings would seem consistent with those of Keenan and colleagues (9) in a similar porcine injury model that indicated a near identical “best PEEP” (determined by tidal compliance) for the supine and prone positions.

There are shortcomings. Very limited gas exchange data are provided. Data regarding ventilation efficiency would have been particularly interesting, as the underlying status of the recruitment/overdistention balance and clinical outcome have been linked more closely to  $\text{CO}_2$ -eliminating efficiency than to improved  $\text{O}_2$  exchange (10). Likewise, no detailed information regarding hemodynamics or  $\text{O}_2$  delivery were provided, even though PEEP titration in either position may be limited by its effects on hemodynamics.

Numerous unresolved bedside questions remain regarding prone positioning. In whom is it most likely to prove effective and helpful? Convincing data, such as supplied here, regarding the more

homogenous distribution of stress and strain in the prone position would argue for prone ventilation as a method of preventing ventilator-induced lung injury. Thus far, however, clinical data have demonstrated a convincing benefit only in those patients who already suffer from severe lung injury (11). Is proning indicated for lung protection even when there is no benefit to oxygenation and ventilation pressures are modest? Conversely, one could imagine an adverse effect of proning in such patients, particularly given the higher “dose” of critical care often associated with prone ventilation in the forms of sedation and neuromuscular blockade. If proning is to be an integral part of a generalized “lung protective” strategy, when is it safe to withdraw it? Are the mechanisms of oxygenation benefit always tied to recruitment? Perhaps not; a variety of vascular disturbances have long been reported in ARDS (12, 13) (and have recently been well described in coronavirus disease [COVID-19]). In that context, it is interesting to note that prone position also results in a more homogenous distribution of perfusion (14, 15).

Although guidelines and tables provide some useful guidance for general populations, bedside decisions for the individual are made most confidently when based on a firm mechanistic understanding and close monitoring of the relevant variables. The study by Katira and colleagues helps unravel the interactions between PEEP and prone positioning and suggests that the complexity of the mechanical problem posed by protecting the injured lungs of life-threatening ARDS can be reduced a bit by applying titrated PEEP in the prone position.

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## Where Is the Cystic Fibrosis Transmembrane Conductance Regulator?

Cystic fibrosis (CF) is a mucoobstructive pathology associated with chronic inflammation and chronic bacterial infection of the lungs. Mutations in the CF gene lead to dysfunction of the CFTR (CF transmembrane conductance regulator) and development of clinical symptoms. Two central characteristics of CF lung disease are an inadequate hydration and a defective transport of the mucous layer that covers and protects the airway surface. Despite the huge progress made in CF care, the exact relationships between primary defects and different manifestations of the disease are lacking. In that context, it is important to establish a precise map of CFTR expression along the airways. Such studies, begun immediately after the discovery of the CF gene, gradually concluded that CFTR was detected in airway surface epithelial cells, including in airway multiciliated cells, as well as in rare “CFTR hot” cells near or within airway submucosal gland acini or gland duct cells (1, 2).

In 2018, Montoro and colleagues (3) and Plasschaert and colleagues (4) applied single-cell RNA sequencing (scRNAseq), a technology that allows unbiased transcriptional profiling of tens of thousands of individual cells. They generated a catalog of the cells expressed in the lung, and, more particularly, they revealed a population of rare cells that they entitled pulmonary ionocytes. This name reflected a population of cells found in fish gills and frog skin, which contribute to ion homeostasis and hydration. Interestingly, pulmonary ionocytes were not only established by Montoro and colleagues and Plasschaert and colleagues as the sites of highest CFTR expression in airway cells but

were also characterized by their high expression of other ion-transport genes, including subunits of the amiloride sensitive Na<sup>+</sup> channel, and components of H<sup>+</sup>-ATPases. This peculiar gene expression program, also showing similarities with renal intercalated cells, suggests that ionocytes could be directly involved in active absorption of fluids (5) and/or regulation of acid-base homeostasis (6). In the murine tracheal epithelium, the majority of CFTR was present in pulmonary ionocytes but basal and secretory cells also expressed CFTR (3). Remarkably, little to no CFTR expression was detected in multiciliated cells, which were thought to be the main harbor of CFTR expression.

In this issue of the *Journal*, Okuda and colleagues (pp. 1275–1289) are now providing a comprehensive description of CFTR-expressing cell types in normal human conducting airways (7). To do so, they have combined scRNAseq technologies, single-cell quantitative RT-PCR, and RNA *in situ* hybridization methods, validating some of their results by electrophysiological approaches. Their measurements also provide information about variations of gene expression between large and small airway epithelia. This work confirms that CFTR is strongly expressed in ionocytes but also underlines the rarity of these cells in human small airway epithelium. The authors' conclusion is that ionocytes represent a fraction of the total CFTR signal. Instead, more abundant cell types that express lower individual levels of CFTR represent a much larger fraction of the total signal. Secretory cells are thus the dominant cell type that expresses CFTR in the surface epithelium of large and small airways. CFTR is also significantly expressed in basal cells, suprabasal cells, and, to a lesser extent, multiciliated cells. Finally, the authors directly measured CFTR-mediated Cl<sup>-</sup> secretory function, demonstrating a better correlation between this signal and the presence of secretory cell types than with ionocytes. Secretory cells from CF airway epithelia, but not multiciliated cells, were capable of CFTR-mediated Cl<sup>-</sup> secretion after transduction with wild-type CFTR.

The results of Okuda and colleagues fit well with independent data sets that were recently published on human lung and airway (Table 1). Deprez and colleagues provided an scRNAseq atlas of 77,969 cells from 35 healthy human airway samples derived from 10 subjects, in which they defined 28 distinct cell types/states (8). They confirmed the high

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