One of the most provocative observations is that, by stereology measures, smokers do not appear to have an increase in AM numbers. This is in conflict with studies demonstrating an increase in BAL macrophages from smokers (12). Interestingly, prior data support the authors' present observation, suggesting that the extent of the response in BAL was overrepresented by an analysis in lung tissue sections (13). Though not directly explored in this study, a possible explanation for these divergent findings is that AMs from smokers may be easier to lavage during BAL, thereby increasing their measured numbers. Alternatively, the authors identified that IMs were increased in smoker lung tissue, which appeared to be mostly due to an increase in macrophages in the alveolar septum. The role of the IMs in this setting were not clearly defined but these data do suggest the potential importance of defining IM function in exposure conditions like cigarette smoke and, ultimately, in disease states like chronic obstructive pulmonary disease.

In total, this study continues to expand on our understanding of macrophages based on lung tissue location. It offers tantalizing insights into further tissue specification of macrophages and suggests that more work needs to be done, both to identify tools for isolation but also to focus on macrophage functions in these distinct regions. Ultimately, further work in these areas will allow the research community to truly grasp the diverse functional roles of macrophages with a goal of being able to tune these functions to limit tissue damage and/or injury and mitigate chronic lung disease. ∎

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∂ A Physiological Point of View on Expiratory (Re)action during Mechanical Ventilation

A commonly held belief about avoiding ventilator-induced lung injury primarily takes into account the inflation half-cycle, whereas deflation is considered to be a passive process about which very little can be done to influence the lung function of patients (1). Is this belief actually correct? We know that patients should be ventilated without harming the lung (so-called protective lung ventilation)

(2). This may be achieved by combining low V_T with the correct amount of positive end-expiratory pressure (PEEP) to minimize the mechanical load on the ventilated lung. However, mechanical ventilation is different from the physiological mechanism that mammals use for gas exchange, in which the inspiratory flow is obtained by the negative pressure generated by the inspiratory muscle. Expiration is often believed to be passive and determined by the elastic recoil pressure of the lung, as it is during physiological ventilation. Unfortunately, expiration is not an exclusively passive phenomenon. The diaphragm not only acts as an inspiratory muscle but also exerts a braking action aimed at slowing down the expiratory flow (3). The absence of this brake, as in the case of patients with paralysis, is responsible for much more rapid lung

emptying. This may adversely affect gas exchange because an end-inspiratory pause has been shown to improve gas exchange to a greater extent than an end-expiratory pause (4). Furthermore, the action of the diaphragm during expiration should be preserved because faster expiration could lead to additional lung collapse and the development of atelectasis (3).

In this issue of the *Journal* (pp. 1218–1229), Pellegrini and colleagues (5) propose a novel research technique that applies concepts from respiratory physiology to mechanical ventilation. The primary purpose of this study was to determine if the application of continuous external expiratory resistance is able to maintain the beneficial effects of diaphragm expiratory braking in terms of optimization of lung mechanics, prevention of expiratory flow limitation (EFL), and avoidance of lung collapse. To evaluate this, the authors inserted different resistors with the capability of slowing expiratory flow in the expiratory limb of a ventilator connected to pigs with induced mild acute respiratory distress syndrome (ARDS). The experiment was performed at various PEEP levels during both spontaneous breathing and mechanical ventilation (5). One of the main virtues of this study is the complexity and the wide range of the data obtained, including, among other measurements, esophageal pressure, expiratory electrical activity of the diaphragm, and analysis of the computed tomographic scan of the lung during expiration (5).

This deep analysis of the respiratory function allowed the authors to contribute several relevant pieces of information to this field of research. They note a reduction in expiratory transdiaphragmatic pressure during spontaneous breathing and a reduction in expiratory flow and the expiratory time constant, suggesting a more homogeneous ventilation distribution with added resistance. As expected, increased expiratory resistance was associated with a significant reduction of atelectasis during both spontaneous breathing and controlled mechanical ventilation. These results support the hypothesis that the synergistic effects of expiratory diaphragmatic contraction and external expiratory resistance help to avoid lung derecruitment.

As correctly pointed out by the authors, it is time that physicians stop making overcoming airway opening pressure the sole consideration when setting PEEP levels (5). If we strictly consider the effects of PEEP in early expiration, low PEEP is associated with higher expiratory electrical activity and expiratory transdiaphragmatic pressure, but the opposite is true for high PEEP. Hence, the application of different levels of PEEP would seem to play a role in the activation of the diaphragm during expiration that could be used to defend against the collapse of lung units.

However, understanding the phenomenon turns out to be much more complicated. Interestingly, the authors considered another fundamental aspect of respiratory pathophysiology: the presence of EFL. They showed that the expiratory flow was significantly reduced by the application of additional levels of external expiratory resistance (5). The presence of EFL can indicate increased inhomogeneity of ventilation (6), which is generally attributed to cyclic opening–closure of the relatively small airways, leading to the generation of abnormal shear stress. This stress is responsible for mechanical and histological damage in bronchioles with an accompanying increase in airway resistance (7). Recently, we found that EFL is common in ICU patients (48%) within the first 72 hours of ICU stay (8) and, furthermore, that it correlates with adverse outcome. EFL frequently affects patients with chronic obstructive pulmonary disease (COPD), obesity, and heart failure, as well as patients with ARDS, especially at low PEEP (9–11). Mechanisms leading to EFL can vary among patients with different pathologies. Patients with COPD may develop EFL because of decreased elastic recoil pressure, increased expiratory resistance, and airway collapsibility, factors that tend to reduce the diameter of the airways to a point at which expiratory flow is maximal. On the one hand, this implies that to achieve complete expiration, patients should increase their FRC, so-called intrinsic PEEP (12, 13). On the other hand, some patients can experience a decrease in their FRC, such as those with severe obesity, spinal cord injury, fluid overload, or ARDS (8, 10, 11, 14, 15). The reduced FRC has the potential to increase both the expiratory resistance and the possibility of collapse of the small airways.

In light of these findings, what can we learn from this experimental study? The use of a resistor on the expiratory limb seems promising from the clinical point of view. However, we need to know which level of resistance is most effective and if that level should vary among patients with acute respiratory failure of different etiologies; for how long this technique should be used; and finally, in which patients this device should be recommended and in which it could be harmful. For example, what would be the role of a resistor in patients with an increased FRC, as occurs in patients with COPD? According to the traditional physiological approach, the use of this device would further increase intrinsic PEEP by limiting lung emptying. Would it be more effective in those patients in whom the FRC is reduced? Although further clinical studies are needed to clarify this question, we believe that industries should implement ventilators with a modified expiratory valve controller to obtain the most physiological ventilation possible. ∎

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Three Steps to Cure Pulmonary Fibrosis
Step 1: The Runaway Train or Groundhog Day?

If idiopathic pulmonary fibrosis (IPF) is to be cured, then it is likely that the "fibrosis" will need to be identified before it has led to widespread architectural destruction of the parenchyma. Unfortunately, by the time IPF is diagnosed, most patients have suffered symptoms for a number of years (1) and have considerable physiological abnormality, with reduced FVC and gas transfer ($D_{L_{CO}}$) and irreversible loss of lung function (2).

Therefore, step one on the path to cure IPF requires that early precursor lesions must be identified in presymptomatic individuals at a point at which the natural history can be positively altered. We've all seen the movie: the runaway train barreling down the tracks but somehow the hero manages to divert the course.

In the last decade, a number of studies assessing radiological changes in longitudinal cohorts of people without obvious IPF-identified parenchymal changes, referred to as interstitial lung abnormalities (ILAs), have demonstrated an increase in both all-cause mortality and mortality from pulmonary fibrosis (3, 4), raising the prospect that ILAs may be the precursor lesions for IPF. Furthermore, there is overlap in the genetic architecture of IPF and ILA (5), and, indeed, serum biomarkers associated with pulmonary fibrosis are associated with ILA (6). This raises two fundamental questions: *1)* are ILAs a precursor lesion for IPF and, if so, *2)* should at-risk populations be screened for them?

I started to write this editorial on Groundhog Day (February 2, 2020), and folklore suggests that the groundhog's shadow can lead to its prediction of the duration of winter; however, the phrase has come to epitomize the futility of trying to change the future even when you know what is going to happen. This could be an even greater concern when the future is less than certain. The prevalence of ILA is high, between 7% and 9% of screened populations (4), which would suggest that if ILAs were indeed precursor lesions, the incidence of IPF should be much higher than currently reported (7, 8). Will identification of ILAs offer us the chance to save the runaway train or will it just lead to a Groundhog Day of recurrent harm associated with lead-time bias–related anxiety or adverse effects associated with overdiagnosis?

In this issue of the *Journal*, studies by Salisbury and colleagues (pp. 1230–1239) and Hunninghake and colleagues (pp. 1240–1248) provide data that help inform the answers to these two crucial questions (9, 10). Both these studies use computed tomography scanning to "screen" unaffected first-degree relatives of patients with familial pulmonary fibrosis (FPF), and the study by Hunninghake and colleagues also screens first-degree relatives of patients with sporadic IPF. Both studies used a similar definition of ILA, and the rates of observed ILA in relatives of patients with FPF were similar across the cohorts (23% of the Vanderbilt cohort and 26% in the Brigham Cohort). The presence of the minor allele of the *MUC5B* promoter polymorphism rs35705950 and shorter telomeres were associated with ILAs in both cohorts. These data are similar to findings by Mathai and colleagues (11). Although Mathai and colleagues used a different definition of ILA, which they termed preclinical pulmonary fibrosis, they found 18% of first-degree relatives had an ILA, with 15.6% being described as fibrotic and, by the authors definition, preclinical pulmonary fibrosis. They also found an association between the *MUC5B* promoter variant and ILA but not the common variant of *TERT,* although they did not measure telomere length. All three studies showed an association between increasing age and ILAs with the median age of those with an ILA being 58 years (9), 61 years (10), and 65 years (11) compared with those