EDITORIALS

PEEP or No PEEP — Lung Recruitment May Be the Solution

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The acute respiratory distress syndrome (ARDS) is characterized by inflammatory lung injury with alveolar flooding and abnormalities in surfactant function. ARDS (a subcategory of acute lung injury) is associated with the collapse of peripheral lung units, pulmonary infiltrates, stiff lungs, and hypoxemia.[1] The syndrome is both common (with an incidence of about 80 cases per 100,000 population every year) and lethal (with a death rate of more than 38 percent) in a community population of patients with acute lung injury.[2]

Patients with severe ARDS invariably require mechanical ventilation to decrease the work of breathing and to improve oxygen transport. An improvement in oxygenation can be obtained in many patients by an increase in positive end-expiratory pressure (PEEP), a strategy that was suggested in the first description of ARDS about 40 years ago.[3] PEEP can partially reverse the collapse in parts of the lung. This reversal is called lung recruitment[4] (Fig. 1, and the video clip, available with the full text of this article at www.nejm.org).

Despite intense research since the 1960s on the use of PEEP, there is no consensus on how to choose an "optimal" level of PEEP in order to improve survival. Patients who die of acute lung injury usually do not die of hypoxemia but, rather, of the multiple organ dysfunction syndrome,[5] which may be brought on paradoxically by the initially lifesaving ventilatory support.[6] The only therapy that has been shown to reduce mortality is the use of a low tidal volume, which was associated with a decrease in mortality from nearly 40 percent to 31 percent.[6] The decrease probably reflected less ventilator-induced lung injury and, therefore, fewer systemic biochemical and molecular consequences.[7]

Many studies in animals have shown that ventilator-induced lung injury can also be caused by "atelectrauma," the repetitive recruitment and derecruitment that can occur with every breath.[8] This type of injury can potentially be mitigated by the maintenance of lung recruitment through an increase in the level of PEEP. However, a recent large, multicenter trial by Brower et al.[9] demonstrated no difference in the rate of death with the use of higher-level PEEP. There are a number of possible reasons why the use of higher PEEP levels has not demonstrated a decrease in mortality.[9] First, the "dose response" of PEEP may be such that most of the benefit is gained from increasing the pressure from 0 to about 8 cm of water (the PEEP level used in the control group in the study by Brower et al.). Second, the data from studies in animals may not be relevant to humans, perhaps because most studies in animals use lung-injury models that do not capture the critical aspects of human disease.[3] Third, any beneficial effects of PEEP in terms of decreasing injury caused by lung recruitment and derecruitment may have been outweighed by the detrimental effects of PEEP, such as the hemodynamic consequences, or by overdistention of the lungs.

In this issue of the *Journal,* Gattinoni et al.[10] address the third hypothesis by providing direct visual evidence, in addition to previously available physiological evidence,[11] that the capacity for opening (or "recruiting") collapsed lung units varies greatly among patients with ARDS. To the extent that an important effect of PEEP is lung recruitment, or the maintenance of recruitment after a lung-recruitment maneuver, the study by Gattinoni et al. shows that there are many patients with ARDS in whom an increase in PEEP cannot produce much recruitment because

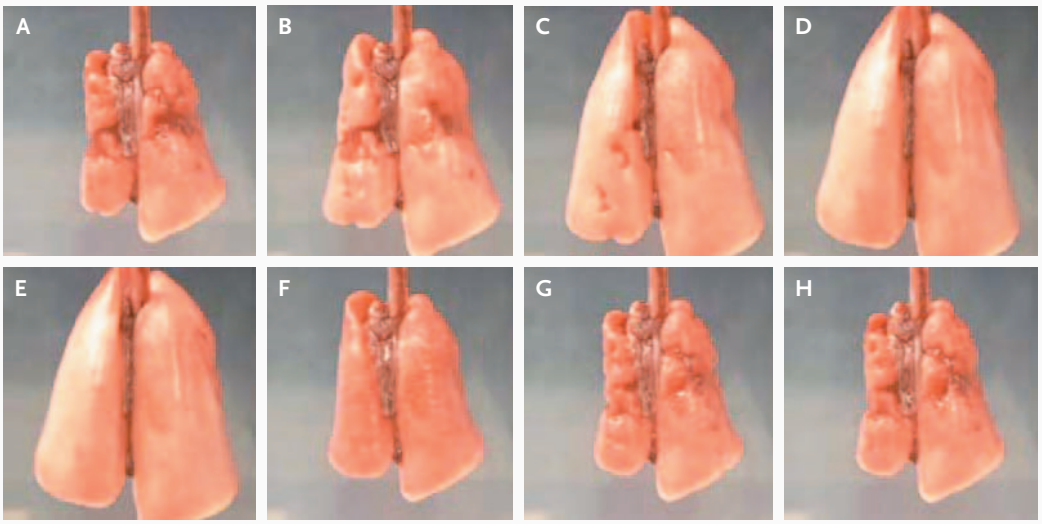

Figure 1. Ventilation of an ex Vivo Rat Lung.

This series of photographs is taken from a video clip of an ex vivo rat lung being ventilated with a tidal volume of 7 ml per kilogram, with and without PEEP. (The video clip, which was also the source of a figure in Slutsky,[4] is available with the full text of this article at www.nejm.org.) All photographs were taken at the end of inspiration. Panel A shows areas of collapse when PEEP is zero. PEEP was then increased to 15 cm of water, and Panel B shows the end of inspiration of the first breath after the change in PEEP. Some of the collapsed areas are now expanded ("recruited"), whereas others remain collapsed, showing the inhomogeneity of alveolar units. Recruitment of previously collapsed units is progressive with time, as shown at three breaths (Panel C) and reaching completion five breaths after the increase in PEEP to 15 cm of water (Panel D). Panel E shows the expanded lungs at a PEEP of 15 cm of water, just before the reduction of PEEP to zero. After one breath at zero pressure (Panel F), there are no areas of gross collapse, but after the third and fifth breaths after the reduction of PEEP (Panels G and H), the lung derecruitment is obvious. This figure demonstrates that it takes many ventilatory cycles for the lung to be recruited and that the maintenance of recruitment requires a relatively high PEEP. In patients, the time for recruitment would usually be much longer than the few breaths shown here, depending on the disease process and the pressures applied. In a clinical setting, the lungs of a patient being ventilated would differ from the rat lung shown here. In the figure, since there is no chest wall, when no PEEP is applied, collapse can occur with each exhalation. In the clinical setting, the chest wall would provide a small end-expiratory inflating pressure, which would prevent some of the collapse shown. However, the basic physiological principles illustrated are probably relevant for patients.

there is very little "recruitable" lung. In such patients, the use of PEEP may cause greater ventilator-induced lung injury by leading to pulmonary overdistention — and hence may actually worsen the clinical outcome. The study also suggests that the percentage of potentially recruitable lung is an important predictor of mortality (as shown in Fig. 4 in the article by Gattinoni et al.[10]). It is not clear, however, whether this finding really is an important independent predictor of mortality or is a reflection of the fact that patients with a greater percentage of potentially recruitable lung simply have more severe underlying lung injury.

The study by Gattinoni et al. also provides a potential solution to the problem of identifying which patients may benefit from PEEP. Their data suggest that computed tomography (CT) of the lungs during a static increase in pressure to 45 cm of water can be used to identify which collapsed lung units have a high potential for reopening. Hence, this approach could be used to identify which patients may benefit from higher levels of PEEP and which patients may potentially be harmed. This hypothesis is attractive, but there are a number of caveats that must be considered. First, the authors defined the potential for recruitment with the use of a pressure of 45 cm of water. It is known that in a number of patients, some lung units do not open at this pressure but do open at higher pressures; hence, the current study underestimates the full potential for recruitment, but it did apply a pressure that is probably reasonably safe in most patients if they are

monitored appropriately. Second, Gattinoni et al. did not address the issue of how much potentially recruitable lung is sufficient for clinicians to consider the use of higher PEEP levels in a given patient. Third, even if a patient is found to have a large amount of recruitable lung, the study does not address how to decide which level of PEEP should be used. Finally, the use of CT is not a pragmatic solution to the calibration of PEEP in most clinical settings. The use of simpler clinical or physiological variables to predict or estimate recruitment has been suggested. In contrast to a previous report by Gattinoni et al.,[12] in the current study, the mode of injury — pulmonary (direct) or extrapulmonary (indirect) — was not helpful in predicting the potential recruitability of the injured lungs. However, data from the current study by Gattinoni et al. and another study[11] suggest that physiological variables (e.g., the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen) may be of greater practical value, even though the sensitivity and specificity of these findings may be less than those of CT. All these issues must be addressed before any of these approaches can come into wide clinical use.

A major message from Gattinoni et al. is that future studies investigating the optimal strategy for the setting of PEEP levels must take into account the degree to which the lungs can be recruited. In this postgenomic era, Gattinoni et al. demonstrate that sound physiological principles are still relevant to our understanding of disease processes. Such principles, along with advances in knowledge of cellular and molecular biology, should lead to improvements in the care of our critically ill patients.

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Antioxidants and the Prevention of Preeclampsia — Unresolved Issues

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Preeclampsia is a pregnancy-specific, multisystem disorder that can have considerable adverse effects on the mother and the fetus. In developing countries, preeclampsia is a major cause of death among pregnant women.[1] In the United States, 15 percent of premature births and their attendant complications are attributable to preeclampsia.[2] Thus, numerous strategies intended to prevent preeclampsia — such as the use of antiplatelet agents and supplementation with calcium — have been studied, but without success.[3,4]

More recently, antioxidants have been proposed as a potential preventive strategy on the basis of data suggesting that endothelial dysfunction is