Peak Airway Pressure: Why the Fuss?*

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HFJV = high-frequency jet ventilation; Palv = alveolar pressure; PAP = peak airway pressure; Paw = airway pressure; PCIRV = pressure-controlled inverse-ratio ventilation; Ppl = pleural pressure; Pplat = plateau pressure; PPV = positive-pressure ventilation; VALI = ventilator-associated lung injury

The management of a patient with respiratory failure involves two important, and at times conflicting, goals: providing sufficient ventilatory support to maintain adequate oxygenation and carbon dioxide elimination, and avoiding factors that may cause injury to an already failing respiratory system. These goals, though straightforward in concept, are often difficult to achieve in practice. The physician must often weigh whether the potential beneficial effect of changes in such variables as tidal volume, flow rate, and positive end-expiratory pressure on gas exchange are outweighed by the potential risk of further insult to the lungs. In order to make such an assessment, the physician must understand the mechanisms by which lung injury occurs during mechanical ventilation.

This review will focus on two forms of ventilator-associated lung injury (VALI): barotrauma and acute lung injury. In its broadest sense, the term “barotrauma” refers to pressure-related injury developing in any of a number of tissues; as used most commonly by the clinician, however, the term refers to subcutaneous emphysema, pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema occurring in association with positive-pressure ventilation (PPV). Although barotrauma is undoubtedly the more recognized, feared, and certainly talked about complication of PPV, there is increasing awareness that mechanical ventilation can also cause acute lung injury.1,2

There is a long-standing and widely held belief that high peak airway pressure (PAP) is the most important cause of VALI. High PAP is a common cause for alarm among physicians, nurses, and respiratory therapists caring for the critically ill. Indeed, the belief that high PAP is detrimental to the lungs has been a motivating force behind the development and use of nonconventional modes of ventilation, such as high-frequency jet ventilation (HFJV) and pressure-controlled inverse-ratio ventilation (PCIRV). However, there is a growing body of evidence indicating that lung volume, or, more precisely, lung overdistention, is the important variable contributing to VALI. The goal of this article is to address this issue: Is high PAP injurious to the lung, or is it simply sometimes a marker for lung overdistention, the latter being the real culprit producing VALI?

Relationship Between Airway Pressure and Lung Volume

If measurements of airway pressure (Paw) accurately reflected lung volume changes, it would be clinically irrelevant whether pressure or volume were the important variable determining the occurrence of VALI. In this section, I briefly review the relationship between Paw and lung volume during PPV. The reader should note that most often during PPV, Paw does not truly represent “airway pressure;” rather, Paw generally represents the pressure within the ventilator itself.

The pressure acting to distend (and potentially damage) an alveolus is the transmural pressure; that is, the alveolar pressure (Palv) minus the pleural pressure (Ppl) (strictly speaking, it may be the difference between Palv and interstitial pressure that determines whether lung injury occurs). When there is no gas flow, Paw equals Palv, and Paw therefore becomes a measure of one of the two relevant pressures determining alveolar distention. When airflow is present, Paw differs from Palv by a quantity that varies with the flow rate and degree of airflow resistance. The lower the flow-resistant pressure loss (ie, the lower the flow rate and the lower the airflow resistance), the more closely Paw approximates Palv. As an example, when a decelerating flow pattern is used (such as in pressure-cycled ventilation), Palv increases throughout inspiration, and the difference between Palv and Paw progressively decreases until Palv becomes equal to Paw at end-inspiration.

The foregoing discussion indicates that the accuracy with which Paw reflects Palv depends upon the magnitude of flow-resistive pressure losses in both the airways and the ventilator circuit. From the relationship discussed above, however, we can see that there is another important variable, Ppl, that can alter the relationship between pressure changes measured at

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the airway and changes in lung volume. During mechanical ventilation, Ppl can be affected by a number of factors, including inspiratory and expiratory muscle activity and changes in rib cage and abdominal compliance. Thus, for example, when inspiratory muscle contraction lowers Ppl, a large tidal volume may be associated with a very low Paw. Likewise, large changes in Paw can be associated with small changes (or even decreases) in lung volume when Ppl is significantly increased (as in coughing or “bucking” the ventilator).

To summarize, Paw equals Palv when flow is absent, and Paw only approximates Palv when flow-resistive pressure losses are low. However, even Palv provides no meaningful information about the forces acting to distend the lung unless concomitant changes in Ppl are accounted for.

**Barotrauma**

The case for high PAP as a cause of barotrauma is based almost entirely on circumstantial evidence. A number of human studies have documented an association between the incidence of barotrauma and high PAP. In a retrospective study, Kumar et al. reported that in patients ventilated with a tidal volume (VT) of 12 to 18 ml/kg, barotrauma developed in 6 of 31 patients with a PAP greater than 36 cm H2O, but in only 1 of 34 patients with a PAP less than 36 cm H2O. Petersen and Baier prospectively studied the incidence of barotrauma in 171 patients. They found that barotrauma occurred in 10 of 23 patients (43 percent) with a PAP greater than 70 cm H2O, in 4 of 53 (8 percent) patients with a PAP between 60 and 70 cm H2O, and in no patient with a PAP less than 60 cm H2O. Woodring retrospectively studied 15 patients with ARDS. In that series, the incidence of barotrauma was high: 13 of 15 patients ultimately developed barotrauma, and of those, 12 had a PAP greater than 40 cm H2O.

Despite such reports of an association between PAP and barotrauma, there are several problems with the conclusion that high PAP causes barotrauma. First, the correlation between PAP and barotrauma has not always been as strong as in the studies cited above. Barotrauma can occur at extremely low levels of PAP. In a retrospective study by Rohlffing et al. of 6 of 38 patients with barotrauma had a PAP less than 25 cm H2O. Other investigators have reported a complete absence of barotrauma despite very high levels of PAP. In a preliminary study (published only as an abstract), Leatherman et al. found that in 42 patients undergoing PPV for respiratory failure secondary to asthma, there were no cases of barotrauma despite a PAP value as high as 110 cm H2O in some individuals and a mean PAP of 68 cm H2O for the group as a whole (it is probably no coincidence that the absence of barotrauma in this series occurred in a setting in which flow-resistive pressure losses were high and Paw bore little relationship to Palv). Some reports have actually demonstrated an inverse relationship between PAP and the incidence of barotrauma. Mathru and coworkers compared the incidence of barotrauma during controlled mechanical ventilation and intermittent mandatory ventilation (IMV) and found that there was a lower incidence of barotrauma during IMV (7 vs 21 percent) despite a higher mean PAP (51 vs 34 cm H2O). Clevenger and colleagues converted 15 patients from conventional PPV to HFJV for “hypoxic salvage.” During conventional PPV, the mean PAP was 92 cm H2O, but none of the patients experienced barotrauma. After conversion to HFJV, there was a marked reduction in PAP (to a mean of 41 cm H2O), yet 7 of the 15 patients developed barotrauma within 21 h of conversion to HFJV. Finally, Tharratt et al. converted 31 patients with adult respiratory distress syndrome (ARDS) in whom conventional mechanical ventilation had failed to PCIRV. Although PAP decreased by a mean of 20 cm H2O, 8 of the patients developed barotrauma during PCIRV.

Second, the incidence of barotrauma has been reported to correlate not only with PAP, but with VT as well. Bone et al. found a 40 percent incidence of barotrauma in 50 patients with ARDS. The mean VT in patients developing barotrauma was 22 ml/kg, whereas the mean VT in patients without barotrauma was 17 mg/kg. The following year, after adopting a strategy that minimized VT (mean VT, 11 ml/kg), Bone reported that barotrauma occurred in only 4 of 106 patients (3.8 percent).

Third, large increases in Paw are often associated with large increases in lung volume, but in most studies to date, no assessment of lung volume changes was made that would allow one to distinguish between the effects of high PAP and those of lung overdistention. For example, in the aforementioned studies by Woodring and Petersen and Baier demonstrating an association between high PAP and increased incidence of barotrauma, no mention is made of the VT used. A recent prospective study by Williams et al. did attempt to separate the consequences of high PAP and overdistention of the lung. The authors looked at risk factors for barotrauma and hypotension in 22 patients with asthma undergoing mechanical ventilation and found that of numerous ventilatory variables, including PAP, the only variable with a threshold level predictive of barotrauma was end-inspiratory lung volume, a measure of dynamic pulmonary hyperinflation.

By dissociating pressure changes from volume changes, two animal studies provide important insight into the pathogenesis of pulmonary barotrauma. Polak and Adams found that dogs in which the respiratory system was inflated to a pressure of 80 mm Hg for 10
s developed extensive pulmonary interstitial and mediastinal emphysema, as well as widespread systemic air embolism. In contrast, when each animal’s chest and abdomen were tightly bandaged, thereby limiting lung expansion, application of the same pressure produced no barotrauma. More recently, Caldwell et al. applied a series of 5-s pulses of pressure to the airway of anesthetized rabbits, some of which had undergone thoracic binding to limit lung inflation. In unbound rabbits, the incidence of barotrauma was proportional to the magnitude of the pressure applied at the trachea, but in bound animals, there was no correlation between barotrauma and tracheal pressure. Although mean tracheal pressure was lower in the unbound animals, the incidence of barotrauma was higher in this group, and, as would be expected, mean lung volume was also much greater in the unbound animals. These authors concluded, much as did Polak and Adams, that airway pressure itself did not cause barotrauma. It should be noted that in both of the aforementioned studies Paw may have equaled Palv, but because increased Ppl accompanied abdominal and thoracic binding, Palv reflected neither transalveolar pressure nor lung volume.

**Acute Lung Injury**

In humans, it is virtually impossible to distinguish between histologic and functional abnormalities caused by mechanical ventilation and injury caused by the underlying disease process that necessitated mechanical ventilation in the first place. Hence, our knowledge of acute lung injury resulting from mechanical ventilation is based almost exclusively on animal studies. As with barotrauma, a number of studies have demonstrated an association between high PAP and acute lung injury. The specific focus here, however, will be on the relatively few studies that have separated pressure-related effects from volume-related effects.

Egan examined the effect of a 40 cm H₂O distending pressure on lung solute permeability in rats. In one group of animals, the pressure was applied to an entire lung, whereas in the other group, the pressure was applied through a catheter wedged into a segmental bronchus, thereby limiting the pressure to a portion of the lung. When only a portion of the lung was distended, there was a 6- to 12-fold increase in the volume of the distended region; when the same pressure was applied to the entire lung, there was only a 3- to 4-fold increase in lung volume. The greater volume change occurring when only a portion of the lung was subjected to the distending pressure was attributed to the ability of the alveoli to expand by compressing nearby nondistended lung tissue. In association with the greater volume change, alveolar protein permeability increased in the group in which the applied pressure was limited to a portion of the lung, whereas there was no change in alveolar permeability in the whole-lung group. The author concluded that lung volume rather than applied pressure caused the lung to become permeable to protein.

Dreyfuss and coworkers compared the effects in rats of high VT ventilation, achieved by both PPV and negative-pressure ventilation (NPV), with those of normal VT but high airway pressure ventilation (achieved by thoracoabdominal binding). Both high-VT groups developed marked pulmonary edema associated with histologic evidence of endothelial cell detachment and hyaline membrane formation. Despite a much lower airway pressure, the histologic changes were more pronounced in the high-VT NPV group than in the high-VT PPV group. Although the animals undergoing thoracoabdominal binding had PAP values comparable to those of the high-VT PPV group, the lungs from the former group were completely normal. These investigators concluded that “edema was solely related to changes in lung volume and not in airway pressure.” Similarly, Hernandez et al. studied the effects on microvascular permeability of ventilating bound (via a whole-body cast) and unbound rabbits at three different levels of airway pressure. On gross examination, at the two higher levels of airway pressure, the lungs of the unbound animals showed areas of hemorrhage and atelectasis and developed several localized air leaks. The lungs of the casted animals, however, were completely normal. The unbound animals developed a progressive rise in the capillary filtration coefficient, reaching a value 650 percent above baseline at the highest level of airway pressure. In the bound animals, there was no significant change in permeability, even at the highest level of airway pressure.

Although the studies cited above in no way represent an exhaustive review of the literature relevant to mechanical ventilation and acute lung injury, they do constitute a representative sample. Thus, whether a study end point has been macroscopic lung appearance, histologic evidence of acute lung injury, or functional measurements such as alveolar permeability, studies that have separated the effects of pressure and volume have found lung overdistention, not high airway pressure, to be the underlying cause of lung injury.

**Implications for Patient Management**

By considering a few representative clinical scenarios, we can gain insight into how the evidence and principles reviewed thus far apply to patient management.

**The Patient With a Tensely Distended Abdomen**

When abdominal compliance is decreased, a given change in lung volume is associated with a larger increase in Ppl, and thus a greater pressure change at
the airway is necessary to inflate the respiratory system. In this setting, however, the transmural pressure across the alveolus should be no different than if abdominal compliance were normal, and the risk of VALI should not be increased unless excessive Vrs are used. In such a patient, high PAP does not reflect the degree of lung inflation, and maneuvers to lower PAP, though perhaps not harmful, are probably unnecessary. This situation is in some ways analogous to the previously discussed experimental models using thoracoabdominal binding, which demonstrated that high PAP alone is not associated with lung injury. However, there is an important distinction to be made between thoracoabdominal binding and abdominal distention. In contrast to the global impediment to lung inflation with thoracoabdominal binding, abdominal distention represents a regional impediment to lung inflation, so that some portions of the lung, such as the upper lung zones, might become overdistended, thereby increasing the likelihood of injury.

An Asthmatic Patient With Respiratory Failure

In this setting, the distinction between pressure and volume as the cause of lung injury is crucial because the goal of reducing PAP may directly conflict with the goal of minimizing pulmonary hyperinflation. Tuxen and Lane have shown that in patients with severe airflow obstruction requiring mechanical ventilation, PAP does not necessarily reflect the degree of pulmonary hyperinflation. They demonstrated that although a reduction in Vr causes both PAP and hyperinflation to decrease, a reduction in inspiratory flow rate causes PAP to decrease at the same time that hyperinflation increases. These investigators also showed that the degree of circulatory depression (assessed by blood pressure) is directly correlated with the degree of hyperinflation. As previously mentioned in the section on barotrauma, a prospective study from the same institution showed hyperinflation, but not PAP, to be predictive of barotrauma and hypotension in asthmatic patients undergoing mechanical ventilation. This is also consistent with at least one prior study demonstrating a complete absence of barotrauma in mechanically ventilated asthmatic patients despite very high PAP. Thus, the management of respiratory failure in a patient with severe airflow obstruction should focus on providing the minimum Vr and minute ventilation consistent with acceptable (but not necessarily normal) gas exchange, and on using a sufficiently high inspiratory flow rate to allow adequate time for exhalation. A management strategy that focused on the avoidance of high PAP would use low flow rates, thereby promoting worsening hyperinflation and increasing the risk of barotrauma and hypotension.

The Patient With Respiratory Failure Secondary to ARDS

As demonstrated by Munder et al, ARDS affects the lungs in a patchy fashion with areas of consolidated lung interspersed with areas of normal or near-normal lung. As several authors have noted, the "normal" Vr used in this setting may be distributed primarily to the relatively small areas of normal parenchyma, resulting in overdistention and potential injury to these regions. Hence, an important goal in the management of patients with ARDS is to avoid overinflation of remaining normal lung tissue. Unfortunately, at present, there are no guidelines to follow to ensure that a given pattern of ventilation does not cause some regions of the lung to become overdistended. There are, however, some reasonable management strategies.

On the basis of the fact that a static transpulmonary pressure of 35 to 40 cm H₂O inflates the normal human lung to total lung capacity, Marcy and Marini have suggested that peak alveolar pressure (recall that this is not synonymous with PAP) not exceed this level (for a comprehensive discussion of the relationship between alveolar and airway pressure, see the recent reviews by Marini and Ravenscraft). As demonstrated by Egan, however, a pressure that is tolerated when the entire lung inflates may cause injury when only a portion of the lung inflates. Therefore, even careful adherence to guidelines such as these does not preclude the occurrence of regional overdistention and VALI.

An alternative approach to pressure-limited ventilation is to use smaller Vr during volume-cycled ventilation. Recent studies have demonstrated some success with this strategy. In patients with ARDS, the likelihood of regional overdistention will vary with the amount of remaining normal lung tissue, and thus there are no guidelines that ensure a safe Vr. Since lung compliance should correlate with the relative proportions of normal and diseased lung, a potential (but unproven) approach is to scale Vr in proportion to lung compliance. This approach entails monitoring plateau pressure (Pplat): as lung compliance decreases, Pplat increases, thereby signaling the need to reduce Vr. Unfortunately, the level of Pplat that should prompt a reduction in Vr is unknown.

Some Unanswered Questions

A number of studies have examined the effect of different patterns and rates of inspiratory flow on gas exchange and lung mechanics, but the influence of inspiratory flow rates on VALI has been largely unexplored. Can high flow rates directly injure the lung, or do flow rates influence the incidence of VALI only through their effects on the distribution of ventilation (and regional changes in lung volume)?
Peevy and colleagues examined the effect of inspiratory flow rate on microvascular injury in isolated perfused rabbit lung. At similar Vt, there was no change in permeability at the low flow rate, whereas at the high flow rate, capillary permeability increased significantly. However, the difference in flow rates between the low- and high-flow groups was large: on average, a sevenfold greater flow rate in the high-flow group. It remains uncertain whether these observations apply to the intact animal over the range of flow rates used clinically.

Asynchrony between patient and ventilator may make PPV uncomfortable for the patient. Likewise, the buzzing high-pressure limit alarms that generally accompany such asynchrony cause discomfort on the part of many a physician, nurse, and respiratory therapist. But is patient-ventilator asynchrony truly a risk factor for barotrauma? When a patient attempts to exhale while a ventilator delivers a positive-pressure breath, is he risking lung injury? While there is no definite answer to this question, the principles reviewed thus far suggest that unless asynchrony leads to hyperinflation (through breath-stacking), the high airway pressures will be associated with normal trans-alveolar pressures, and therefore should not be harmful.

There are many other important questions that remain unanswered. For example, what are the relative roles of peak lung volume and mean lung volume in causing VALI? From a practical perspective, what is the best way of avoiding or limiting overdistention of normal parenchyma during PPV in patients with ARDS? Is there a difference in the incidence of VALI between pressure-controlled and volume-controlled ventilation (assuming that both modes focus upon avoiding lung overdistention)?

**SUMMARY**

The preponderance of evidence indicates that high airway pressure is not by itself injurious to the lung. Rather, overdistention of the lung appears to be the fundamental mechanism underlying VALI. The physician must bear in mind the factors (i.e., flow-resistive pressure losses, respiratory muscle activity, and abnormalities in rib cage or abdominal compliance) that may alter the relationship between PAP and lung volume. Under some circumstances, high PAP may, in fact, reflect lung overdistention, and maneuvers that minimize overdistention may also reduce PAP. Similarly, the goal of improving oxygenation may sometimes entail strategies (such as prolonging inspiratory time) that lower PAP. In these settings, however, the reducton in PAP should be regarded as a by-product of achieving another therapeutic goal and not an end point in and of itself. In other settings, such as the mechanically ventilated patient with severe airflow obstruction, measures that lower PAP by reducing inspiratory flow rate may worsen pulmonary hyperinflation, and thereby increase the risk of complications.

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