Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure

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Abstract

Mechanical ventilation is used to sustain life in patients with acute respiratory failure. A major concern in mechanically ventilated patients is the risk of ventilator-induced lung injury, which is partially prevented by lung-protective ventilation. Spontaneously breathing, nonintubated patients with acute respiratory failure may have a high respiratory drive and breathe with large tidal volumes and potentially injurious transpulmonary pressure swings. In patients with existing lung injury, regional forces generated by the respiratory muscles may lead to injurious effects on a regional level. In addition, the increase in transmural pulmonary vascular pressure swings caused by inspiratory effort may worsen vascular leakage. Recent data suggest that these patients may develop lung injury that is similar to the ventilator-induced lung injury observed in mechanically ventilated patients. As such, we argue that application of a lung-protective ventilation, today best applied with sedation and endotracheal intubation, might be considered a prophylactic therapy, rather than just a supportive therapy, to minimize the progression of lung injury from a form of patient self-inflicted lung injury. This has important implications for the management of these patients.

Keywords: ventilator-induced lung injury; hyperventilation; gas exchange; noninvasive ventilation

Mechanical ventilation (MV) is usually considered to be a supportive therapy, and is often life saving. However, over the last 15+ years, there has been great emphasis placed on minimizing the risk associated with MV, especially an entity referred to as ventilator-induced lung injury (VILI) (1). The delivery of so-called lung-protective ventilation has been shown to reduce this risk and improve outcomes in patients with the acute respiratory distress syndrome (ARDS). We argue here that a similar process of lung injury, resulting from an injurious breathing pattern, may be at play in many patients with hypoxemic respiratory failure—especially those who have high respiratory drive—even though they are not intubated or ventilated, and hence not subject to injury induced by a ventilator. In the context of this high respiratory drive, lung-protective ventilation might be viewed as not simply a supportive therapy, but as a prophylactic therapy to mitigate patient self-inflicted lung injury (P-SILI). This has a number of important implications for the management of these patients, and expands the concept of VILI into a more global vision of ventilation-induced lung injury.

We start by summarizing the current understanding of interactions between ventilation and lung disease.

VILI

The recognition of VILI has been essential for our understanding of the interactions between ventilation and subsequent lung injury (1–3). We have been able to measure, analyze, and understand the forces applied to the lungs (the transpulmonary pressure, or stress) and the resulting deformation (strain), at the same time taking into account the protection offered by recruiting the lung and keeping it open (4). We have convincingly demonstrated that protective ventilation can reduce VILI and improve prognosis (5). Building on this background, investigators now question the limits of "protective ventilation" (e.g., 6 ml/kg of predicted body weight), and are examining whether additional reductions in tidal volume, exploiting techniques for CO_2 removal, can help improve outcomes further (6).

We have also explored the association of prognosis with possible physiological "markers" that identify risk of injury, such as the driving pressure (7). Driving pressure

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is the ratio of tidal volume to tidal respiratory system compliance, the latter being a crude marker of lung volume (7). Monitoring this parameter appears to be a physiologically sound approach in patients with ARDS, rather than simply relying on the ratio of tidal volume to predicted body weight, which is an index of a patient's healthy lung size. Whether this approach is a better way to set ventilation strategy has yet to be determined.

Spontaneous Breathing during MV

Investigators and clinicians are now concerned by the impact of spontaneous ventilation during MV for ARDS. Experimental studies directly demonstrated that spontaneous ventilation superimposed on MV may worsen lung injury (8, 9). Clinical data demonstrate that use of neuromuscular blocking agents decreases biotrauma (10) and improves physiological and clinical outcomes (11).

There are three possible pathways explaining how spontaneous breathing can be injurious and facilitate the progression of lung injury.

1. Even if "normal" lung can tolerate very large increases in tidal volumes and minute ventilation for short periods of time, as occurs during strenuous exercise, lungs with pre-existing injury are more susceptible to ventilation-induced lung injury (i.e. "two-hit" concept).
2. Based on classical physiologic concepts, the transpulmonary pressure swings (i.e., the stress on the lungs) are similar for a given tidal volume (starting at the same lung volume), whether generated by a mechanical ventilator, spontaneous effort, both, or negative-pressure ventilation (12, 13), as illustrated in Figure 1. However, there are several subtleties that can lead to lung injury in patients with injured lungs, related to the regional distribution of injury, with associated differences in local transpulmonary pressures and local stress (9, 14). Regional increases in transpulmonary pressure are not always well reflected by a global measurement of tidal volume or transpulmonary pressure. The pendelluft phenomenon is a good example, in which a strong effort can induce intrapulmonary redistribution of gas, even before the start of insufflation because of regional (local) forces. A pendelluft can then be observed (i.e., a movement of alveolar air from one region of lung to another without a gain in tidal volume). It is important to remember what we learned from imaging during prone position: although the lung in ARDS seems to be separated into aerated, poorly aerated, and nonaerated areas (the baby lung concept), the "closed," nonaerated areas in the lung can be reopened, depending on how much local force is applied. When patients are placed in the prone position, the pleural pressure gradient changes, as do other forces. As a result, this modifies the anatomical parts of the lungs that are open and aerated. Spontaneous breathing, by locally exerting pressure on "closed" areas, can also reopen certain part of the lungs, explaining the pendelluft phenomenon.
3. During controlled ventilation, alveolar pressure is higher than end-expiratory pressure throughout most of the respiratory cycle; during spontaneous ventilation, however, alveolar pressure can drop well below end-expiratory pressure (12). Increased transmural pulmonary vascular pressure in the context of an increased vascular permeability greatly increases the risk of pulmonary edema through vascular leakage (15). Increases in pulmonary transmural vascular pressures have also been shown to worsen VILI (16). During inspiratory efforts, intrathoracic pressure becomes negative, and the intrathoracic blood volume increases. During these efforts, the intravascular pressure measured in pulmonary intrathoracic vessels decreases, but to a lesser extent than the esophageal or pleural pressure, resulting in increased transmural pulmonary vascular pressures (17). Examples of the effects of negative pleural pressure are given by negative-pressure pulmonary edema occurring in normal lung when airway resistance is increased to a very high level (18), and by the abundant literature on airway resistance–induced lung edema (19, 20). Therefore, negative alveolar pressures created by larger changes in pleural pressure, and therefore positive changes in transvascular pressure, favor lung edema, a mechanism that is amplified with increased vascular permeability.

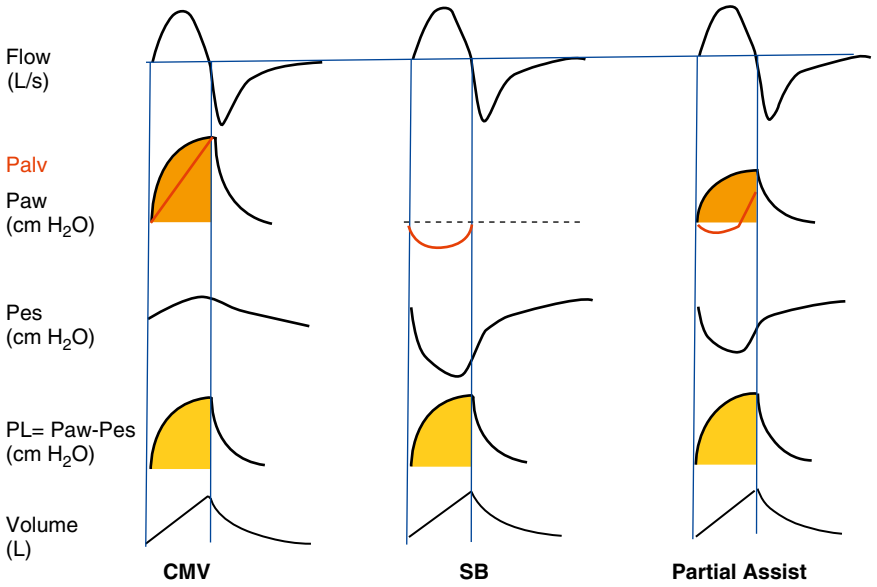

Figure 1. Illustration of how the same transpulmonary pressure can be generated by a mechanical breath during controlled mechanical ventilation, a spontaneous breath, or a combination of the two during partial ventilatory support. From *top* to *bottom*: flow, alveolar pressure (in *red*) and airway opening pressure, esophageal pressure, calculated transpulmonary pressure, and tidal volume. *Vertical blue lines* delimit inspiration time. CMV = controlled mechanical ventilation; Palv = alveolar pressure; Paw = airway opening pressure; Pes = esophageal pressure swings; P_L = transpulmonary pressure; SB = spontaneous breath.

Therefore, under certain circumstances, pathway descriptions 2 and 3 explain that the same transpulmonary pressure swings may be more injurious in lungs with pre-existing injury during spontaneous breathing than during controlled MV.

Nonintubated Patients

Despite numerous studies, the success of noninvasive ventilation (NIV) in (nonintubated) patients with hypoxemic respiratory failure has been limited, with the suspicion that benefit may only be possible in a few selected patients; concerns have also been raised that intubation after failure of NIV is associated with a particularly poor prognosis (21). Importantly, patients failing NIV have been shown in one study to have high tidal volumes before intubation (22); in addition, progressively higher tidal volumes during NIV predict the need for intubation (23). Interestingly, controlling tidal volume in these patients seems almost impossible during NIV (23), suggesting that the patients' respiratory drive, not the ventilator, is predominantly responsible for large tidal volumes in this setting. It is well known that intubated patients with ARDS with very high respiratory drive require high levels of sedation (and often paralysis) to decrease tidal volumes to a presumably safe level. Thus, NIV *per se* may be simply facilitating the development of large tidal volumes in patients with very high respiratory drive.

Do these patients develop lung injury due to the increased tidal volumes and minute ventilation in the absence of intubation, in a manner similar to VILI? This seems possible—and indeed probable. Albert (24) has postulated that, during spontaneous (or mechanical) ventilation, there may be an interplay between ventilation, surfactant dysfunction, atelectasis, and atelectrauma, which leads to ventilation-induced lung injury. In sheep breathing spontaneously, increases in tidal volumes (and minute ventilation) caused by injection of sodium salicylate into the cisterna magna induced lung injury (25). Intravenous injection of small doses of endotoxin in humans has a strong effect on the respiratory drive, independent of fever or symptoms (26). Finally, examples exist of patients without pre-existing lung injury who develop lung injury associated with hyperventilation (27).

Thus, in some patients, lung injury due to increased tidal volumes and ventilation may occur during spontaneous breathing, initiated by a high respiratory drive, which, in turn, lead to lesions that appear similar to the VILI observed in mechanically ventilated subjects (Figure 2). In these patients, the large spontaneous tidal volumes may be viewed as causing injury, and hence any therapy that minimizes generation of these large tidal volumes should be viewed as a prophylactic therapy to avoid the progression of lung injury. This is best accomplished today by intubation, sedation, paralysis, and lung-protective MV, although one could imagine other means in the future.

In addition, a strong indicator of ARDS severity is the ratio of dead space to tidal volume (28), which has a direct and strong influence on minute ventilation. In the nonintubated patient, nasal delivery of heated and humidified O_2 at high flow rates is the only practical means of reducing physiological dead space (22). Whether the survival benefits observed with this approach are explained by a reduction in dead space—and therefore by a reduction in ventilatory need (and drive)—is an attractive hypothesis that would also fit well within the context of P-SILI.

Why Do We Have So Little Evidence?

It took many decades to recognized that MV caused clinically important lung injury; this long delay in recognition likely occurred because the added injury due to MV took place in the context of patients who were already diagnosed with ARDS, and thus was attributed to worsening of the underlying disease process. This difficulty is also true in nonintubated patients, but, in addition, the lack of monitoring of ventilatory variables in nonintubated patients makes assessment much more difficult. Nonetheless, the limited observations of very large tidal volumes during NIV are consistent with the hypothesis of existing P-SILI (23).

MV as a Necessary Protection

Based on the thesis described previously here, when spontaneously breathing patients have high respiratory drive that leads to increased minute ventilation with high tidal volumes, a goal of therapy must be to minimize this P-SILI. Intubation and a lung-protective ventilatory strategy, guided by lung injury severity, including elevations in dead space, may be the easiest, most efficient way to achieve this goal. For example, in the study by Mascheroni and colleagues (25), in which sheep were injected with sodium salicylate in the cisterna magna, the animals that were then sedated, paralyzed, and mechanically ventilated developed no pulmonary abnormalities, as opposed to the animals that were allowed to breathe spontaneously

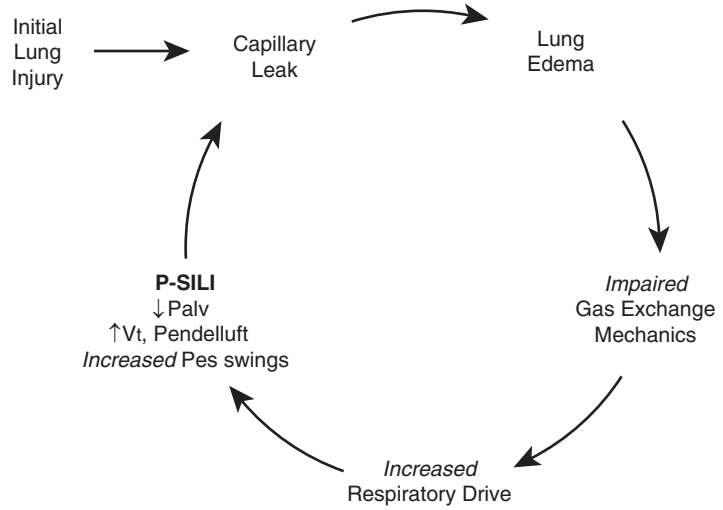

Figure 2. Illustration of the vicious cycle of injury present in patients with acute respiratory failure. Palv = alveolar pressure; Pes = esophageal pressure swings; P-SILI = patient self-inflicted lung injury.

and that developed lung injury, decreased compliance, and pulmonary infiltrates.

In applying these concepts, what are the key issues?

1. It is important to ascertain whether the spontaneously breathing patient in fact has a high respiratory drive and has adopted a ventilatory pattern that will lead to subsequent lung injury. This is not a trivial matter. Some receptors in the lung may act to limit end-inspiratory lung volumes (e.g., Hering-Breuer reflex), although it is unclear when they are playing an important role (29, 30). Other receptors, such as the juxta-capillary receptors, may stimulate respiratory drive (31). If the lung-protective reflexes are overwhelmed by stimulant factors increasing respiratory drive (e.g., metabolic acidosis, anxiety, etc.), then treatment to decrease the increased ventilation must be taken. Whether reducing the work of breathing by delivering ventilation proportional to patients' needs will facilitate lung protection is an interesting hypothesis, suggested by some animal and human data (32, 33). Intubation and controlled MV is, however, today the simplest approach to protecting the lung. MV by itself can control the load, leading to increased respiratory drive; however, when a high respiratory drive is principally caused by lung receptor stimulation, metabolic acidosis, or delirium, ventilatory assistance may only minimally affect the drive, and sedation may have little effect on this drive.
2. This concept of P-SILI may help us to better define the role and targeting of treatments directed toward controlling respiratory drive or CO_2 load, including extracorporeal CO_2 removal. In both nonintubated and intubated patients, better monitoring of spontaneous breathing seems necessary, including measurement of respiratory drive (e.g., occlusion pressure or P0.1 [34]), tidal volume, and perhaps respiratory muscle activity (esophageal pressure [35], diaphragmatic activity [36, 37]).
3. Over the last 20 years, we have learned to minimize VILI during MV. It is possible that, by applying the same principles, MV can be used "prophylactically or early" to protect the lung from P-SILI. As such, under defined conditions, MV, far from being just supportive or even damaging, becomes a true preventive measure to stop the progression of lung injury and perhaps prevent ARDS. MV is not the only option for P-SILI. For instance, extracorporeal lung support therapies are also viable options to protect the lungs, whereas the key question is how to balance the tradeoffs between P-SILI, the complications of extracorporeal circuits, and the side effects of intubation/MV.

Finally, the arguments presented above highlight the clinical relevance of basic physiological concepts in the clinical context, and, specifically, can help clinicians better acknowledge the importance of preventing severe lung injury and ARDS by application of an effective prophylactic therapy. Hopefully, this will lead to greater implementation of lung protection for both our intubated and nonintubated patients, especially those with ARDS (38). ■

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