Editorial

Protecting lungs during spontaneous breathing: what can we do?

Hong-Liang Li[1], Lu Chen[2,3], Laurent Brochard[2,3]

[1]Department of Critical Care Medicine, Peking University Third Hospital, Beijing 100191, China; [2]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada; [3]Keenan Research Centre and Li Ka Shing Knowledge Institute, Department of Critical Care, St Michael's Hospital, Toronto, Canada

Correspondence to: Laurent Brochard. 209 Victoria Street, Toronto, Ontario, M5B 1T8, Canada. Email: BrochardL@smh.ca.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Yoshida T, Nakahashi S, Nakamura MA, *et al.* Volume Controlled Ventilation Does Not Prevent Injurious Inflation During Spontaneous Effort. Am J Respir Crit Care Med 2017. [Epub ahead of print].

Submitted Jul 25, 2017. Accepted for publication Jul 27, 2017.
doi: 10.21037/jtd.2017.08.25
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.25

Ventilator-induced lung injury (VILI)

Shortly after stepping into the new millennium, VILI raised extensive attention among clinicians when implementing mechanical ventilation for supporting or treating patients with acute respiratory failure. A wide awareness of the clinical importance of VILI resulted from a large randomized control trial in acute respiratory distress syndrome (ARDS) conducted by the ARDS Network (1). This landmark trial tamped down the causal link between VILI and outcomes that had been suggested by a series of classic experimental studies since 1970s (2) and an indispensable clinical study on lung protective ventilation in 1998 (3).

Minimize VILI during passive ventilation

Different hypotheses on the mechanisms of VILI have been proposed and tested in numerous studies (2). We now have strong evidence showing that excessive stretch of alveoli (overstretch) is a key mechanism in developing VILI (4). The widely-adopted lung-protective ventilation therefore emphasizes limiting tidal volume at 6 mL/kg of ideal body weight and plateau pressure less than 28–30 cmH_2O—an effective strategy to reduce the risk of VILI and improve clinical outcomes in mechanically ventilated patients with different causes (1,5,6). A recent analysis on thousands of patients enrolled in clinical trials further showed that driving pressure [i.e., the difference between the end-inspiratory plateau pressure and end-expiratory pressure or positive end-expiratory pressure (PEEP)] is the strongest known parameter in respiratory mechanics associated with survival rate (7). Comparing with the tidal volume normalized by ideal body weight (ideal functional lung size), driving pressure reflects the tidal volume normalized by respiratory compliance (a reasonable estimate of the functional lung size). Hence, it is physiologically sound to limit driving pressure as a target of lung protection, although this needs to be tested in future clinical trials. One fact, however, must be emphasized: clinical trials aiming to minimize VILI were designed for or conducted in patients mostly under passive ventilation (sedated with or without being paralyzed). We don't know whether so-called lung protective ventilation remains "protective" in patients during spontaneous breathing. In addition, limiting tidal volume or driving pressure in patients with spontaneous effort can be challenging due to patient-ventilator interaction interfering with the measured parameters.

Patient self-inflicted lung injury (P-SILI)

Before we discuss how to better protect lungs during spontaneous breathing, one important question is whether spontaneous breathing can induce lung injury. Our answer is, yes (8). Indeed, two studies in 1988 have already suggested or demonstrated this link. One was a classic study by Dreyfuss *et al.* (9), showing that high tidal volume

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generated by negative pressure ventilation in animals also led to pulmonary edema as observed during passive positive pressure ventilation. This was not spontaneous breathing but the pressure profiles were close to what could be observed with negative pressure generated by inspiratory muscles. The other study was from Mascheroni *et al.* (10). By injecting sodium salicylate into cisterna magna of sheep, Mascheroni and his colleagues demonstrated that spontaneous hyperventilation without mechanical ventilation can lead to lower compliance, hypoxemia, and morphologic lung injury similar to that was observed in VILI. In other words, once lungs are overstretched, the injury can develop regardless the source which originated this repeated distension. Interestingly, this injury didn't develop after paralysis with fully controlled ventilation. In this regard, positive-pressure ventilation provided by ventilators is not the "evil" comparing with negative-pressure ventilation provided by inspiratory muscles. Instead, mechanical ventilation can protect lungs from P-SILI (11).

Minimize P-SILI during spontaneous breathing

Minimizing P-SILI can be achieved through at least two approaches. One could be a complete elimination of spontaneous effort (12). This approach is simple and can be effective, but can also result diaphragm atrophy by disuse of the respiratory muscles. Obviously, one cannot always keep patients in passive ventilation. This means that one eventually needs to use positive ventilation superimposed to patient's spontaneous effort, i.e., assisted ventilation. To optimize ventilatory strategy in this situation, we first need to find out a reliable parameter of respiratory mechanics to assess lung overstretch at the bedside. Ideally, lung strain (lung deformation related to their original size) appears to be the "best" quantity to assess lung overstretch. Assessment of lung strain however requires lung volume measurement which may be infeasible in reality (13). Alternatively, lung stress (internal force per area experienced by lungs) can be used as a surrogate. Lung stress (tensile stress) is usually scaled by transpulmonary pressure—the difference between airway pressure and pleural pressure. Pleural pressure is usually estimated by esophageal pressure, which can be obtained through placing an air-filled catheter into esophagus (14,15). This technique, despite its usefulness, has not been implemented in clinical practice except in a few centers (16). Clinicians often replace transpulmonary pressure with airway pressure to assess the risk of lung overstretch irrespective of the variety in chest wall mechanics. This is sub-optimal but might be acceptable when airway pressure is the only external force stretching lungs (i.e., during passive ventilation) and the alteration in chest wall mechanics is not significant. During spontaneous breathing, respiratory muscles also apply force (negative pleural pressure) on the lungs. The huge variability in this negative pleural pressure makes that the airway pressure delivered by the ventilator is far from representing the transpulmonary pressure. For this reason, the difference between peak airway pressure and PEEP in pressure-target mode cannot be taken as an approximation of driving pressure. Direct measurement of airway plateau and driving pressures during spontaneous breathing is possible but requires transiently relaxed respiratory muscles while performing an end-inspiratory hold. This operation is not allowed in some brands of ventilators and the measurement is not always reliable.

Instead, if we assume the lung compliance do not change at the moment of recovering spontaneous breathing, restricting tidal volume (the product of lung compliance and the tidal change in transpulmonary pressure) should be equivalent to limiting the tidal change in transpulmonary pressure. Briefly, tidal stress should be limited when tidal volume is controlled. This was supposed to be hold during both passive ventilation and spontaneous breathing. Indeed, Bellani and his colleagues demonstrated that if the volume and flow are comparable, the tidal change in transpulmonary pressure is similar between passive ventilation and spontaneous breathing (17).

So how do we limit tidal volume during spontaneous breathing? An intuitive answer is using volume-targeted mode. Volume-targeted mode can set flow rate by decreasing applied airway pressure when a patient generates inspiratory effort (negative pleural pressure); whereas pressure-targeted mode increases flow rate to maintain a preset airway pressure (14). In other words, volume-targeted mode can still limit tidal volume during spontaneous breathing whereas pressure-targeted mode would provide higher tidal volume. From this standpoint volume-targeted mode appears to be superior to pressure-targeted mode. The situation, however, becomes much more complicated once asynchronies occur. For example, if patient's inspiratory effort is strong and long, double triggering often occurs (15). Double triggered breaths (or breath-stacking, either in case of high respiratory drive or through reverse

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triggering) make tidal volume almost doubled in volume-targeted mode. Nevertheless, volume-targeted mode might provide a strict control in tidal volume and transpulmonary pressure for regular breaths, regardless of the magnitude of spontaneous effort. Using volume-targeted mode was therefore hypothesized as a potential approach to minimize P-SILI. This hypothesis, though sounds plausible, has not been tested until very recently.

New messages from Yoshida's study

Yoshida and his colleagues (18) applied volume control ventilation in rabbits and pigs with injured lungs (repeated lavage). They directly measured pleural pressures (in addition to esophageal pressure) at dependent and non-dependent regions of the lung by placing a thin, flat balloon into pleural space. The esophageal pressure, which is an indirect measurement of pleural pressure, was simultaneously measured. The overall tidal volume and the tidal change in transpulmonary pressure estimated by esophageal manometry were controlled in both spontaneous breathing and passive ventilation, as expected. Surprisingly, volume controlled ventilation failed to limit the tidal change in transpulmonary pressure at dependent lung regions during spontaneous effort, which became comparable to pressure controlled ventilation (18).

So why the transpulmonary pressure estimated by esophageal manometry differs from that at dependent lung measured by pleural balloon? Is this discrepancy simply caused by technical barriers such as pressure transmission? Most likely, it is not the case. A first important fact, which is frequently ignored, is that the distribution of pleural pressure is not uniform. Experimental studies have demonstrated the presence of a vertical gradient of pleural pressure from top to bottom in all postures, probably related to gravitational forces from the weight of lungs and mediastinal tissues (19,20). This vertical gradient becomes greater in injured lungs (20). Human studies have also indirectly confirmed this vertical gradient (21). Hence, what we measured pleural pressure (directly or indirectly) usually represent a local pleural pressure for a local region. For example, esophageal pressure represents the local pleural pressure at the middle lung region at supine position (20), which can be explained by the anatomic position of esophagus. While there is a vertical gradient in the absolute value of pleural pressure, however, the tidal change in pleural pressures were found to be similar in different regions of normal lungs during both spontaneous breathing and passive ventilation (22). Hence, the tidal change in transpulmonary pressure calculated by the esophageal pressure was deemed to be a reliable representative for "global" change in transpulmonary pressure (20,22).

Yoshida's study (18), however, found this is not the case in injured lungs. During spontaneous breathing, the tidal change in pleural pressure at dependent lung is significantly greater than at the middle lung (esophageal pressure). Consequently, the tidal change in transpulmonary pressure (tidal lung stress) at dependent lung became greater than at the middle lung. Volume control ventilation hence didn't prevent high regional lung stress and injurious inflation pattern (regional gas distribution) such as "pendelluft" reported in pressure control ventilation (23). This important finding advanced our knowledge that the dependent region of injured lung can be overstretched by spontaneous effort even when the tidal volume (global lung stretch) has been limited at 6 mL/kg. To explain the difference in regional stress distribution between injured lungs and normal lungs, Yoshida and his colleagues proposed that "*injured lung tissue exhibits solid-like behavior in contrast to the fluid-like behavior of normal lung tissue*". Of note, both high regional lung stress and "pendelluft" have been linked with lung injury by the same group of researchers (24). Moreover, the excessive regional lung stress at dependent lung was eliminated only when strenuous inspiratory effort was suppressed by paralysis in Yoshida's study (18). This may well be one of the reasons why eliminating spontaneous effort by administration of neuromuscular blocking agents at the early stage of ARDS can improve survival in patients who already received volume controlled ventilation (12).

Conclusions

Yoshida's study advanced our understanding on regional respiratory mechanics during spontaneous breathing. The main result denied the hypothesis that volume controlled ventilation would safely prevent lungs from P-SILI. Moreover, conventional parameters including tidal volume, driving pressure or even esophageal pressure may underestimate the regional stress at dependent lung. This makes the assessment of the risk of P-SILI more challenging in clinical practice. Nevertheless, one should bear in mind that what Yoshida tested is a specified volume control ventilation with a relatively low preset flow (<30 L/min) and a low PEEP (3–10 cmH_2O). The

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door of optimizing ventilator settings and modes to reduce P-SILI remains open. Back to a physiology standpoint, seeking for a ventilatory strategy to minimize P-SILI with preserved spontaneous effort should not and will not stop.

Acknowledgements

None.

Footnote

Conflicts of Interest: L Brochard's laboratory has received equipment or grants from Medtronic Covidien, Philips, General Electric, Air Liquide, Fisher Paykel, and Maquet. HL Li and L Chen have no conflicts of interest to declare.

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Cite this article as: Li HL, Chen L, Brochard L. Protecting lungs during spontaneous breathing: what can we do? J Thorac Dis 2017;9(9):2777-2781. doi: 10.21037/jtd.2017.08.25

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