



Transpulmonary Pressure to Guide Mechanical Ventilation: Art or Science?

The pressure required to move the respiratory system and generate a breath in spontaneously breathing subjects is *negative* and is produced by the contraction of the respiratory muscles; in patients on controlled mechanical ventilation, it is *positive* and is generated by the ventilator (1). Considering inertia nihil, the pressure required to generate a breath 1) comprises the pressure to overcome resistance and elastance of the respiratory system; 2) is partitioned among the different components of the respiratory system (i.e., lung and chest wall); and 3) is generated by the gradient developed across the different components of the respiratory system (“transmural pressure”) (Figure 1) (1).

We learned that ventilatory strategies minimizing the pressure applied to the lung (i.e., transpulmonary pressure [P_L]) can decrease mortality (2). On the basis of the assumption that the pressure across the respiratory system (Prs) closely approaches P_L, protective ventilatory settings are obtained, limiting Prs to a maximal value of 30 cm H₂O (2). However, Talmor and colleagues found that only 24% of the variance in P_L was explained by Prs, whereas 52% was due to variation in chest wall pressure (P_w) (3). Several studies confirmed these observations (4, 5), leading to the suggestion that assessment of P_L instead of Prs should be considered to optimize protective ventilatory strategies (2).

The most used method to provide an indirect determination of P_w uses an air-containing latex balloon sealed over a catheter placed in the esophagus and transmitting balloon pressure to a transducer (esophageal pressure [Pes]) (1). Recent studies highlight the potential clinical relevance of using measurements of Pes to estimate P_L. Grasso and colleagues suggested that positive end-expiratory pressure (PEEP) should be titrated to reach a maximal value of 20 cm H₂O of P_L instead of a maximal value of 30 cm H₂O of Prs (4). Recent clinical trials tested the hypothesis that alveolar collapse and hypoxemia may be determined by negative values of P_L caused by high P_w and that, therefore, setting PEEP to maintain a *positive* P_L might optimize alveolar recruitment, minimizing the risk of hyperinflation and of hemodynamic impairment (6, 7). Central in this hypothesis is the assumption that the absolute value of Pes would provide an estimate of P_w accurate enough to allow a clinically relevant assessment of P_L. The first single-center trial enrolled 61 patients and found that the ratio of the partial pressure of arterial oxygen to the F_IO₂ at 72 hours was 88 mm Hg higher in the Pes-guided group than in the control group (95% confidence interval, 78.1–98.3; *P* = 0.002) (6). The second multicenter trial enrolled 200 patients. The primary outcome, a ranked

composite score incorporating death and ventilator-free days among survivors through Day 28, was not different between groups (7).

In this issue of the *Journal*, Sarge and colleagues (pp. 1153–1163) present a *post hoc* analysis of the latter trial (8). The authors found that Pes-guided PEEP was associated with lower mortality among patients with lower Acute Physiology and Chronic Health Evaluation-II (APACHE-II), having the opposite effect in patients with higher APACHE-II. Moreover, in patients without shock or hypotension at baseline, Pes-guided PEEP was associated with more days free of shock and of ventilator support. By contrast, in patients with vasopressor-dependent shock at baseline, Pes-guided PEEP was associated with fewer shock- and ventilator-free days. The relevance of the observation that, independent of treatment group or multiorgan dysfunction severity, mortality was lowest when PEEP titration achieved end-expiratory P_L near 0 cm H₂O should not escape our notice (8). Despite the intrinsic limitations of a retrospective, *post hoc*, not prespecified analysis, and the fact that the APACHE score does include variables not directly related to organ failure, these data seem to suggest that measurements of Pes may allow replacing Prs with P_L as a tool to set ventilator settings and that targeting an end-expiratory P_L nearer 0 cm H₂O might enhance lung protection.

Years ago, the clinical use of Pes was proposed by clinical physiologists (9) that Berwick would define as “visionary innovators” (10). However, because clinicians tend to adopt innovations very slowly, to introduce Pes in the clinical practice, the scientific community still needs “to move to sort through ambiguous evidence, proceed to collaboration within a community of observers, and finally move to consensus for action” (11). According to the German philosopher Immanuel Kant (12), “actions are acceptable only if everyone could do or could receive it.” Under these circumstances, several steps need to be taken to make measurement of Pes acceptable according to Immanuel Kant’s view. First, Pes measures a *local* value of pressure, while P_w is not uniform (13), and therefore, relating overall lung volume and P_L to a local value of P_w may be misleading (13). Moreover, whereas Pes in upright subjects closely reflects absolute values of P_w, in supine or semirecurrent postures, absolute values of Pes do not accurately assess absolute values of P_w and may be largely different, depending on gravitational forces and the lung–chest shape (13). Terragni and colleagues performed direct measurements of P_L outside the thorax (during *ex vivo* lung perfusion “before” lung transplantation) and indirect measurement of P_L using values of Pes of the same lung inside the thorax (after lung transplantation) (14) and suggested that a correction factor of 5 cm H₂O should be subtracted from the measured values of Pes to have a correct estimate of absolute Pes (14). Rigorously conducted studies are therefore needed to assess the validity of absolute or corrected values of Pes that should be used to calculate P_L. Second, future clinical trials should use enrichment strategies to optimize selection of patients who may benefit the most from the use of a Pes-guided ventilatory strategy and eventually randomize only patients with a severe impairment of the elastic properties of the chest wall as assessed by prerandomization measurements of chest wall elastance.

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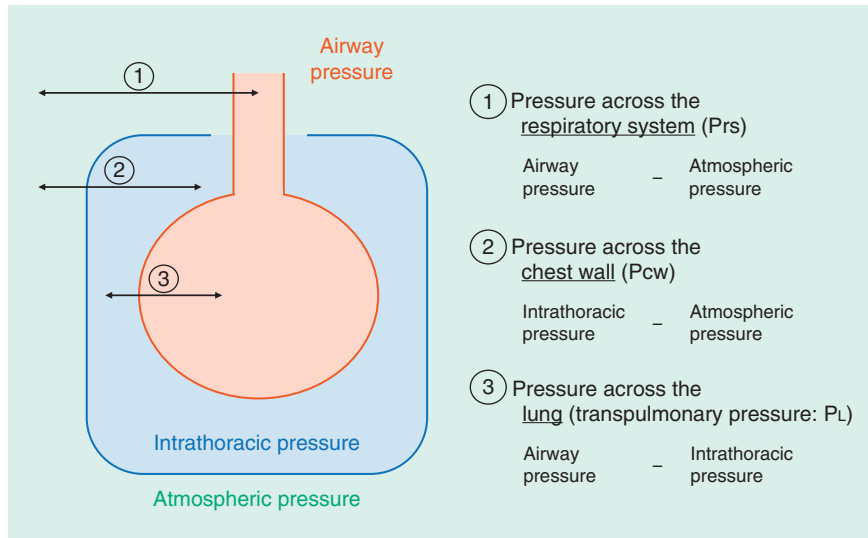


Figure 1. Schematic representation of the relevant positive pressures required during controlled mechanical ventilation to generate a breath and generated by the gradient developed across the different components of the respiratory system (“transmural pressure”).

Third, large, multicenter international observational studies collecting Pes values might be key, but this implies that the physiological meaning and interpretation of Pes should be uniform for all clinicians, and that we must expand the teaching of all technical skills. In case clinical monitors or ventilators implement “automatic” measurement of Pes, we should avoid what is described with the reading and interpretation of “automatic” measurement of pulmonary arterial pressure (15).

In the late 1980s, Joseph Milic-Emili entitled an editorial: “Is weaning an art or a science?” (16). We respectfully allude to his title in this manuscript, knowing that, as far as weaning is concerned, for Pes in clinical practice there is still (as John Lennon and Paul McCartney would phrase it) a “long and winding road” ahead of us (17). ■

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Endobronchial Optical Coherence Tomography for the Diagnosis of Fibrotic Interstitial Lung Disease A Light at the End of the Tunnel?

An accurate diagnosis of fibrotic interstitial lung disease (ILD) is critical to inform prognostication and selection of pharmacotherapy. Clinicians are ideally able to integrate the clinical history, laboratory findings, and morphologic features on chest imaging within multidisciplinary discussion (MDD) to achieve a consensus diagnosis. However, despite this process, a confident diagnosis remains elusive in approximately 15% of patients (1), and there is often a need for additional information to guide management decisions. This diagnostic uncertainty has traditionally prompted consideration of histopathologic evaluation via surgical lung biopsy (SLB), but this procedure is associated with substantial risk of morbidity and mortality (2).

Several novel diagnostic techniques have recently been studied in an attempt to overcome the risks of SLB. For example, transbronchial lung cryobiopsy has a superior safety profile that permits an expanded role in ILD (3, 4), although this procedure still suffers from issues of high interobserver variability and some challenges in implementation (5). More recently, a genomic classifier has emerged as an additional diagnostic tool that reduces the subjectivity commonly associated with interpretation of histopathology; however, this tool still requires tissue sampling and has uncertain utility beyond distinguishing usual interstitial pneumonia (UIP) from non-UIP patterns (6, 7).

Optical coherence tomography (OCT) is the latest addition to this growing list of bronchoscopic tools potentially useful in the diagnosis of ILD, offering a minimally invasive method of high-resolution imaging of the lung parenchyma that avoids the major complications of SLB. Endobronchial OCT employs near-infrared light to visualize surrounding structures with a resolution of $<10\ \mu\text{m}$, approaching the $2\text{-}\mu\text{m}$ resolution of microscopy. Analogous to radial ultrasound, an OCT probe is passed through the working channel of a bronchoscope, generating light that passes through and interacts with circumferential tissue. The resultant backscatter is detected and used to create a cross-sectional image 8 mm in diameter, with subsequent pullback of the probe producing a three-dimensional

reconstruction of sequential images along the path of the selected airway. OCT has been used to assess smooth muscle and airway wall thickness in asthma after bronchial thermoplasty (8, 9), to distinguish early from invasive carcinoma (10), and to identify major cancer subtypes (11, 12).

In this issue of the *Journal*, the report by Nandy and colleagues (pp. 1164–1179) serves as a proof-of-concept study comparing the ability of OCT to distinguish UIP from non-UIP patterns, using SLB as the histopathological gold standard (13). This builds on previous work from the same group that first reported successful use of OCT *in vivo* to identify a UIP pattern in five patients with idiopathic pulmonary fibrosis (14). Impressively, the current study showed sensitivity and specificity of 100% in detecting a UIP pattern, suggesting OCT may have a significant role in the evaluation of fibrotic ILD, potentially relieving much of the historical reliance on SLB.

These are very encouraging findings, but substantial additional work is needed before widespread clinical implementation of this technique (Figure 1). Most importantly, external validation across multiple centers and diverse populations is critical to safeguard against the damage that can arise from ILD misclassification. In addition, larger studies should also evaluate interobserver variability in interpretation and the potential of OCT to identify more specific histopathologic patterns beyond simply separating UIP and non-UIP patterns. These future studies should further evaluate the impact of OCT on clinical diagnosis and diagnostic confidence when employed in the real-world scenario of an MDD. Finally, the clinical impact of OCT in fibrotic ILD should then be assessed, including how its use affects meaningful outcomes such as time to diagnosis and selection of pharmacotherapy.

After the validation of OCT as a reliable diagnostic tool, it will be necessary to optimize its operationalization in a variety of settings. As an advanced imaging technique currently used predominantly as a research tool, successful uptake requires conceptual acceptance of its clinical utility, widespread access to the necessary equipment, and adequate training of both proceduralists and pathologists. Given the impracticality of real-time quality control by an experienced pathologist, proceduralists must achieve competence with OCT to ensure adequate image acquisition during bronchoscopy. This includes selecting imaging locations at multiple anatomic sites, confirming the subpleural location of the OCT catheter before scanning, assessing image quality in real time, and

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