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The Staying Power of Pressure- and Volume-limited Ventilation in Acute Respiratory Distress Syndrome

Titration of mechanical ventilator support is a key modifiable determinant of morbidity and mortality in patients with acute respiratory distress syndrome (ARDS). Limiting V_T and plateau pressure (Pplat) attenuates ventilator-induced lung injury (VILI), extrapulmonary organ failure, and risk of death in ARDS (1). However, uncertainty lingers over whether common clinical targets (e.g., V_T 6–8 ml/kg predicted body weight [PBW]; Pplat 30 cm H_2O or less) are ideal for all patients with ARDS, sparking interest in other bedside measures that might help guide V_T selection, including airway driving pressure (ΔP; ΔP = Pplat − positive end-expiratory pressure [PEEP]) (2). Experimental data suggest other modifiable characteristics of ventilator support also might modulate mechanical lung injury, including PEEP, respiratory rate, and air flow (3–5).

Mechanical power has been proposed as a unifying metric to quantify total VILI risk (6). Mechanical power, which reflects the energy delivered by the ventilator to the respiratory system per unit time, is computed in J/min as 0.098 × respiratory rate × V_T × (PEEP + 0.5ΔP + [peak pressure – Pplat]). This empirical formulation for power is associated with VILI in preclinical models and with mortality in cohort studies (7, 8), but whether it properly weights clinical importance (if any) of each component is uncertain. Moreover, the components of mechanical power often move in competing directions, leaving clinicians who seek to "minimize mechanical power" without a clear bedside strategy. For example, attempts to limit V_T and ΔP will generally reduce V_E, but compensatory increases in respiratory rate can increase power. Increases in PEEP can also cause increases in mechanical power when unaccompanied by adequate reduction in ΔP. Therefore, clinicians using the concepts of mechanical power at the bedside are faced with a challenge: which ventilator parameters are most important to attenuating VILI and improving patient outcomes?

In this issue of the *Journal*, Costa and colleagues (pp. 303–311) explore associations between the often-competing components of mechanical power and mortality (9). The authors address associations between components of power and mortality using data from 4,549 patients with ARDS undergoing controlled mechanical ventilation. Their retrospective analysis included patients from six randomized trials—ranging from early trials of pressure-volume limitation (1) to more recent trials of PEEP titration (10, 11)—as well as observational data from the Medical Information Mart for Intensive Care III single-center electronic health record database from years 2001–2012. Costa and colleagues performed multiple analyses to evaluate the association of 60-day mortality with total mechanical power and its major subcomponents: elastic static power (differentiated by the PEEP component), elastic dynamic power (the ΔP component), and resistive power (the peak pressure minus Pplat component). The authors then used directed acyclic graphs to demonstrate their assumptions regarding pathways of confounding and to choose covariates for models evaluating the association between mechanical power and mortality. Additional mediation analyses using only the randomized trial data explored whether ΔP and respiratory rate mediated associations between randomly assigned pressure-limited ventilation or higher PEEP strategies with mortality.

Results showed that, of all the components of mechanical power, only ΔP and respiratory rate were significantly associated with mortality in the multivariable-adjusted model. From this model, the authors estimated that each 1-cm H_2O increase in ΔP was associated with a fourfold higher mortality risk as compared with each 1 breath/min increase in respiratory rate, yielding an equation (4 × ΔP + respiratory rate) that the authors suggest could be used at the bedside to estimate the relative benefits of changing ΔP or respiratory rate. Only the elastic dynamic component of power (determined by ΔP) was associated with mortality in multivariable models, whereas static and restrictive components were not associated with mortality. In addition, the authors showed that associations between ΔP and respiratory rate with mortality risk were dependent on respiratory system compliance—patients with higher compliance were predicted to benefit slightly more from lower respiratory rates, even at the expense of higher V_T (and higher ΔP), whereas patients with low compliance were predicted to benefit more from a lower V_T (and ΔP) at the expense of high respiratory rates. Results showing ΔP as the primary factor influencing associations between mechanical power and mortality, with a lower contribution from respiratory rate, were supported by a number of sensitivity and

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subgroup analyses, including mediation analysis. The authors provided multiple figures demonstrating predicted "optimal" targets for V_T and respiratory rate across various ranges of lung compliance and dead space.

Strengths of the analysis include the use of multiple randomized controlled data sources over nearly 20 years of research, which allowed the authors to leverage prospective data ascertainment and randomization, which may avoid some misclassification bias and confounding by disease severity in the setting of PEEP and V_T. The use of directed acyclic graphs allows readers to observe the authors' conceptual framework for how covariates and components of mechanical power influence each other and risk of death and allows open debate over if such a framework is realistic. Multiple sensitivity analyses supported the authors' primary findings.

Limitations included the use of data that were largely more than a decade old, with other practices that now may influence mechanical power and mortality (e.g., prone position) in increasing use. Another limitation includes complex associations—both among the components of mechanical power as well as between ARDS severity and the components of mechanical power. For example, changes to PEEP can result in alveolar recruitment or overstretch and can therefore also result in changes to respiratory system compliance, Pplat, peak pressure, ΔP, and, indirectly, respiratory rate. In addition, poorly compliant lungs with high dead space may require higher ΔP and respiratory rates, even with permissive hypercapnia, placing associations between ΔP, respiratory rate, and mortality on shakier causal ground. Lastly, the interactions between sedatives and neuromuscular blockade with the components of mechanical power remain unexplored.

What should clinicians take away from the findings of Costa and colleagues? Their results reaffirm a clinical approach that prioritizes lowering V_T and limiting Pplat (and, consequently, ΔP) in patients at greatest risk of VILI. In practice, such patients are often identified by low respiratory system compliance, precisely the population in whom lower V_T was associated with the largest difference in mortality in their study. In patients with comparatively high respiratory system compliance, (and, consequently, ΔP and lower risk of VILI), risk of death was low and did not differ much with V_T between 6 and 8 ml/kg PBW or respiratory rates across the typical range.

Echoing prior studies (2, 12), results from Costa and colleagues suggest that reducing V_T to below 6 ml/kg PBW might confer additional benefits in patients who have low respiratory system compliance and high ΔP. Attaining V_T of 4–5 ml/kg PBW with acceptable gas exchange appears feasible in many patients without extracorporeal support (13). Yet, in practice, the speculative potential for added lung protection with "ultra-low" V_T must be weighed against risks of deep sedation, neuromuscular blockade, and extracorporeal gas exchange, if necessary, to facilitate tolerance (14).

How best to perform this patient-specific risk and benefit analysis is unclear and remains among the great challenges to realizing precision respiratory support (15). No formula or algorithm can supplant the role of sound and informed clinical judgment guiding bedside decision-making. Still, allowing for individualization, a volume- and pressure-limited strategy remains the foundation of lung-protective ventilation for patients with ARDS. ■

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How Do We Know What We Are Missing? Loss of Signaling through CD148 Drives Fibroblast Activation in Pulmonary Fibrosis

Examination of signaling pathways associated with idiopathic pulmonary fibrosis (IPF) has proven to be complex, and easily identifiable targets with therapeutic efficacy still are lacking (1). Despite the increasing clinical trials dedicated to IPF and other fibrosing interstitial lung diseases and the approval of two antifibrotic therapies, nintedanib and pirfenidone, there is still no curative treatment (2). IPF remains a persistent disease characterized by damaged epithelium, fibroblast/myofibroblast accumulation and activation, excessive extracellular matrix (ECM) deposition, and progressive scarring (3). As our understanding of the pathogenesis has evolved and we recognize fibrosis as a process of aberrant wound healing (4), it is clear that identifying signaling pathways in each cellular population compared with changes seen in whole lung tissue will allow for increased specificity during novel therapeutic development (5). Dissecting out the role of overexpressed genes and pathways in cellular lineages is critical, as the upregulation may be an attempt at a normal repair process with the continued activation driving a fibrotic response. However, absent or downregulated pathways may also end up acting in a profibrotic manner by failing to provide signals of inhibition. This leads us to a critical question: how do we distinguish, find, and activate repair pathways that are missing?

In this issue of the *Journal*, Tsoyi and colleagues (pp. 312–325) examine one such antifibrotic signaling pathway specifically in fibroblasts: the receptor-like protein PTPRJ/CD148 (tyrosine phosphatase-eta) and its ligand syndecan-2 (6). An examination of α-smooth muscle actin–positive myofibroblasts within IPF tissue demonstrated decreased CD148 expression. Therefore, they hypothesized that decreased signaling through this antifibrotic pathway allows for hyperactivated PI3K/Akt/mTOR signaling, reduced autophagy, increased p62 accumulation, and subsequent NF-κB activation (6).

CD148 is highly expressed in the lungs and many other tissues as well as numerous cell lineages, including fibroblasts, endothelial cells, and leukocytes (7–9). It dephosphorylates and regulates proteins involved in fibrosis, including PDGF, EGF, and VEGF (10, 11), by inhibiting growth factor signals and proliferation, and its activation is antifibrotic in a mouse model of radiation-induced fibrosis (9). Interestingly, CD148 is significantly upregulated in synovial monocytes/macrophages in a mouse model of collagen-induced arthritis and in patients with rheumatoid arthritis (12).

In 2011, Whiteford and colleagues identified syndecan-2 as a novel ligand for CD148 (13). Syndecan-2 is one of four syndecans that comprise a family of heparan sulfate (HS) proteoglycans. Each syndecan contains a specific extracellular ectodomain, a conserved transmembrane domain, and a short cytoplasmic domain. Because of the interaction of HS-glycosaminoglycan chains with matrix proteins, cytokines, growth factors, and their receptors, syndecans are important signaling molecules in cancer, angiogenesis, and wound repair (14, 15). Soluble syndecans have been implicated in wound healing processes and are often generated in response to stress and pathogenesis. Syndecan-1 is increased in dermal fluid of mice during wound repair, and syndecan-1–deficient mice have delayed skin wound healing because of defective proliferation and migration of keratinocytes and epithelial cells (16, 17). Syndecan-4 is also significantly increased during dermal repair in mice and humans. It facilitates fibroblast adhesion through fibronectin, integrin interactions, and focal adhesion formation by binding to connective tissue growth factor. Syndecan-4 also interacts with tenascin-C (an ECM protein) during wound closure, and its expression closely regulates matrix contraction, fibronectin response, and fibroblast morphology (18). Syndecan-2 expression is increased during pulmonary fibrosis, is upregulated in the presence of TGF-β, can directly bind and regulate TGF-β through its ectodomain, and is expressed in macrophages and endothelial and mesenchymal cells (19–22). Syndecan-2 has been shown to support fibroblast proliferation, spreading, and attachment through activation of MMPs (23), and its shedding can inhibit angiogenesis through binding to its receptor CD148 on endothelial cells (13, 24–26). Syndecan-2 overproduction by macrophages acts in an antifibrotic manner via inhibition of TGF-β signaling in epithelial cells, thereby promoting the internalization of TGFβR1 and reducing cellular apoptosis. It also reduced fibroblast to myofibroblast differentiation and decreased ECM production (9, 20). Administration of recombinant human syndecan-2 was able to attenuate bleomycin-induced fibrosis (20).

In the current article, the authors extend their previous findings and examine the mechanistic role of CD148–syndecan-2 signaling in fibroblasts during pulmonary fibrosis (6). For the first time, they demonstrate that although syndecan-2 has clear antifibrotic functions, it is unable to exert them because of decreased levels of CD148 in IPF

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