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To Intubate or Not Intubate, That Is the Question

The coronavirus disease (COVID-19) pandemic amplified important controversies in the management of acute hypoxemic respiratory failure. First and foremost, the role of noninvasive oxygenation strategies, such as standard oxygen, noninvasive ventilation (NIV), and high-flow nasal cannula (HFNC), has been greatly debated. Some have warned that spontaneous breathing in the setting of high respiratory drive can worsen lung injury, and thus intubation should be considered prophylactic rather than supportive care (1). In contrast, others have reasoned that the inherent complications of mechanical ventilation, namely immobility, infection, and cognitive impairment, should be avoided with the use of noninvasive oxygenation strategies. They reasoned that these approaches can reduce respiratory effort (2) and render spontaneous breathing noninjurious (3).

Furthermore, if noninvasive oxygenation strategies are used, it remains unclear what approach (NIV, HFNC, or standard oxygen), and in whom, is best. Clinical trials attempting to address this question rely on outcomes such as rates of endotracheal intubation (4–6). In an effort to reduce potential bias, the criteria for intubation are often prespecified, given that the nature of the intervention makes blinding impossible. These criteria are largely based on precedent (5) and tend to have face validity to reflect what a reasonable clinician would agree are clinically relevant thresholds to avoid unnecessary delays of life-saving invasive mechanical ventilation.

In this issue of the *Journal*, Yarnell and colleagues (pp. 271–282) suggest that these intubation thresholds do not reflect everyday clinical practice (7). Using two retrospective cohorts of ICU admissions to academic centers in Boston and Amsterdam, the rate of endotracheal intubation within 3 hours of meeting criteria set forth by a clinical trial (4) ranged from 9% to 13%. Although worsening hypoxia was associated with increased rates of endotracheal intubation, only 17% to 19% of the cohort were intubated within 3 hours of a Pa_{O_2}:FI_{O_2} of <80 in the Boston and Amsterdam cohorts, respectively. Interestingly, the rates of intubation within 3 hours did not seem to vary substantially based on the oxygenation strategy used (NIV, HFNC, or nonrebreather)

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at the time the hypoxia thresholds were met. Finally, in a Bayesian analysis, increasing age, chronic obstructive pulmonary disease (COPD), heart failure, and Black race were associated with decreased probability of endotracheal intubation at any time during the ICU stay after meeting a threshold. In contrast, the use of NIV and increased work of breathing were associated with increased probability of intubation.

There are several limitations to this study. First, these findings reflect the care practices at only two academic centers before the pandemic and may not be generalizable to many ICUs of today. As an example of practice variation, HFNC was more commonly used in the Boston cohort but not as commonly used during the pandemic (8). In addition, it remains unclear whether the individual intubation thresholds, when ignored or unrecognized, lead to worse outcomes in terms of mortality. Because no widely accepted thresholds exist, clinicians may not rely on an individual threshold to initiate invasive mechanical ventilation. Instead, they may rely on clinical trajectory, work of breathing, comorbidities, or additional organ failures, which were not reliably captured in this cohort. Although the decreased use of invasive mechanical ventilation in patients of Black race is concerning, the cohort had very limited racial diversity, and it is unknown if withholding intubation exacerbated disparities in terms of mortality. Finally, the entry criteria for the clinical trial participants (4) were strict and included tachypnea with a Pa_{O_2}:FI_{O_2} < 300 without hypercarbia, which ensured a highly selected group at risk for intubation as opposed to the broad criteria used in this observational study. Indeed, heart failure and COPD were associated with lower probability of intubation, which could be explained by the known efficacy of NIV in the prevention of intubation and mortality in patients with exacerbations of these conditions.

Regardless, if there is a disconnect between the criteria for invasive mechanical ventilation in clinical trials and everyday clinical practice, the pursuit to declare a "winner" for the best noninvasive oxygen strategy just got more challenging. The more important question is if a complex, intuitive, and individualized clinical decision such as initiating invasive mechanical ventilation can or should be protocolized? Prior research has shown that a protocolized approach to sepsis resuscitation (9) or postextubation respiratory support (10) is not better than an astute bedside provider customizing their management for individual patients. After all, critical care providers are dealing with syndromes with substantial heterogeneity and not diseases *per se*.

On the other hand, if nonclinical factors such as race, ethnicity, or socioeconomic status risk the influence of implicit bias on clinical decision making, perhaps an unbiased approach with standardized thresholds is warranted. These thresholds must have clinical relevance in terms of preventing delays that would otherwise lead to harm. Often a first step to define such a threshold is to develop prediction tools or analyze risk factors for failure (11–13), but these studies are in effect predicting clinician behavior and not necessarily clinical need for invasive mechanical ventilation. As shown in this analysis, these bedside clinical prediction tools were no better than simple thresholds based on severity of hypoxia. Given that clinical trajectory may play a role in decision making, perhaps techniques that use discrete-time survival analysis to derive prediction tools from large datasets may have better accuracy (14). However, an important step before proposing widespread use of any derived and validated clinical threshold would be to determine if early warning leads to better outcomes (15). Whether the early intervention used when a clinical threshold is met should include early endotracheal intubation is yet to be determined. ■

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NOTCH-ing up Surface Tension in the Fibrotic Lung

Why does idiopathic pulmonary fibrosis (IPF) occur in a pattern that is peripheral and lower zone predominant? The paper in this issue of the *Journal* by Wasnick and colleagues (pp. 283–299) sheds some light on this question (1). Mechanical stress plays a key role in development, maturation, and fibrogenesis and exerts effects on endothelial, epithelial, and mesenchymal cells (2). IPF is radiographically evident first in lower zone peripheral regions of the lung where stretch is most manifest when negative pressure is applied to the pleural space during spontaneous respiration (3). Wasnick and colleagues have added to our understanding of the pathobiology of IPF in this study through experimental methods that involve cell culture, human IPF lung specimens including precision-cut lung slices, and a murine model of pulmonary fibrosis to show that Notch1 (Notch receptor 1) activation occurs in type 2 alveolar epithelial cells (AEC2s) and leads to both AEC2 proliferation and plasticity, with diminished maturation of SFB (surfactant protein B) and SFC (surfactant protein C) (1). The latter is important because surfactant reduces cell surface tension and prevents alveolar collapse (4). The most compelling evidence for Notch signaling as an early initiator of fibrosis was the finding of enhanced Notch signaling in regions of IPF lung that appeared histologically normal. Recently, blood SFB concentrations were found to be the most predictive of progression of interstitial lung abnormalities (ILAs) in two prospective cohorts (5). It would be of interest to know whether imaging effects on regional collapse observed by Wasnick and colleagues are present in human subjects with progressive ILAs and whether the elevated blood SFB concentrations represent pro-SFB in ILA cohorts.

Although the observations by Wasnick and colleagues contribute to our understanding of IPF, they do not exclude the profibrotic impact of Notch1 activation on other cell types involved in lung fibrogenesis or other mechanoreceptor-mediated mechanisms of Notch1 activation. Notch1 cleavage has the capacity to transform several pulmonary cell types, including fibroblasts, endothelial cells, and, as shown in this study, AEC2s into cells that have a more fibrogenic phenotype. Notch1 signaling has previously been shown to induce lung fibroblast-to-myofibroblast transition, and conditional mesenchymal cell–specific Notch1 knockout mice exhibit diminished lung fibrosis compared with control animals in response to bleomycin (6). This is consistent with the findings that Notch1 signaling liberates latent TGF-β (transforming growth factor-β) through mechanical forces involving αvβ6 and αvβ1 integrins (7). This is clinically relevant because integrin inhibitors to limit activation of TGF-β are being evaluated as a treatment for IPF in the INTEGRIS (Evaluation of Efficacy and Safety of PLN-74809 in Patients With Idiopathic Pulmonary Fibrosis) clinical trial (NCT 04396756). Furthermore, endothelial cell–to–myofibroblast transition via the Jagged1 (Jagged receptor 1)/Notch1 signaling pathway has been implicated during bleomycin-induced pulmonary fibrosis in rats (8). Others have shown using a repetitive bleomycin lung injury model that there is activation of the Jag1 (Jagged canonical Notch ligand 1) ligand in pulmonary capillary endothelial cells adjacent to augmented Notch1 signaling in adjacent perivascular fibroblasts (9). So, it appears that Notch1 signaling may be involved in multiple pulmonary cell types during lung fibrogenesis, as enhanced Notch1 signaling in lung cells from various lineages appears to mediate profibrotic effects.

The concept of aberrant mechanosensitive signaling was recently extended to a failure of normal alveolar AEC2 differentiation. Inhibition of AEC2 differentiation into AEC1s led to pulmonary fibrosis when combined with stretch induced in the postpneumectomy lung (10). It is notable that peripheral distribution of fibrosis progressing centrally over time was observed in this model, similar to that seen in human IPF (10). Notch signaling is required for activation of lineage-negative stem cell progenitor cells, but a subsequent decrease in Notch1 signaling is necessary for these lung progenitors to differentiate into alveolar epithelial cells (11). This is in keeping with the observations of Wasnick and colleagues that diminishing Notch1 signaling was protective in the murine model and in human lung slices that allowed more normal AEC2 differentiation and function after injury.

Mechanical force–induced ligand binding–induced activation of cell transformation to more fibrotic phenotypes is under the influence of ADAM10 (A disintegrin and metalloproteinase domain 10) and ADAM17, which are Ca^{2+}-regulated transmembrane sheddases in proximity to Notch1. Caolo and colleagues recently reported that Notch 1 signaling is activated by shear stress through a mechanism that involves ADAM10 and Piezo1 (piezo-type mechanosensitive ion channel component 1) in endothelial cells (12). Recently, mass spectroscopic approaches identified higher concentrations of *active* ADAM10/17 in IPF lung tissue (13). Indeed, mechanical forces expose the moiety that ADAMs cleave when there is ligand binding to Notch1. This cleavage event liberates Notch1 from the cell membrane and enables its translocation to the nucleus after further

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