# Defining Failure of Noninvasive Ventilation for Acute Respiratory Distress Syndrome: Have We Succeeded?

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The efficacy of noninvasive ventilation (NIV) in the management of acute exacerbations of chronic obstructive pulmonary disease and congestive heart failure is well established (1). Randomized trials have consistently shown the benefits of this intervention on important clinical outcomes such as endotracheal intubation and mortality (1–6). Conversely, the role of NIV in the management of acute hypoxemic respiratory failure (AHRF) and acute respiratory distress syndrome (ARDS) remains controversial (7). Clinical trials have shown conflicting results, with effects ranging from benefit to harm when this strategy was compared with standard oxygen therapy or high-flow nasal oxygen (8–15). Results from systematic reviews and meta-analyses suggest NIV could have a potential benefit in reducing endotracheal intubation and death in patients with AHRF and ARDS (16). Despite the conflicting data, studies providing real-world data have recently shown that NIV is still used as a first-line therapy in up to 15–40% of cases (17–19).

Recent research has highlighted the heterogeneity within the definitions of AHRF and ARDS (20, 21). Heterogeneous subgroups of patients may in part explain the observed variability in the efficacy of NIV across studies (22, 23). Indeed, there are compelling mechanistic and physiologic arguments to explain why there may exist heterogeneity of treatment effect in the application of NIV across patients with AHRF. NIV has the advantage, over other noninvasive oxygen devices, of administering higher levels of positive end-expiratory pressure (PEEP) (5). This can improve the aeriation of atelectatic lung regions, which may result in improved oxygenation and homogeneity of ventilation (5). Furthermore, higher PEEP levels may reduce inspiratory drive and effort in spontaneously breathing patients receiving mechanical ventilation. However, NIV may be associated with harm. For example, not all patients with AHRF respond to higher levels of PEEP (24). Moreover, exaggerated inspiratory efforts during NIV can lead to the delivery of large tidal volumes and transpulmonary pressures, further worsening lung injury (25, 26). Identifying which patients benefit from this intervention and which ones will not represents a key clinical question.

In this issue of *AnnalsATS*, Shu and colleagues (pp. 255–263) describe the results of a multicenter and prospective cohort study performed in 17 intensive care units in China, which sought to explore the association between the etiology of respiratory failure (categorized as pulmonary vs. extrapulmonary) and the risk of NIV failure in patients with ARDS (27). The study included 306 patients with ARDS who received NIV using a facemask interface as a first-line therapy. The primary outcome was NIV failure at 28 days, defined as the receipt of endotracheal intubation. The main findings of the study were that both NIV failure and mortality were more frequent in patients with pulmonary ARDS when compared with extrapulmonary causes. These findings persisted after controlling for baseline potential confounders and in a series of sensitivity analyses. Furthermore, as a secondary objective, the authors derived a predictive score for NIV failure using variables readily available at the bedside. The etiology of ARDS, presence of septic shock, age, nonpulmonary sequential organ failure assessment score, the respiratory rate, and arterial oxygen tension/pressure to fraction of inspired oxygen ratio at 1–2 hours of NIV initiation were associated with NIV failure. The score performed well in a split-sample validation cohort.

The study by Shu and colleagues builds on previous research focused on the identification of early predictors of failure of NIV. Despite extensive research in the field, defining NIV failure is still a major challenge. Indeed, "failure" encompasses a number of different clinical scenarios that ultimately lead to the decision to intubate. Rather than a treatment *per se*, mechanical ventilation acts to support the patient and injured lungs until the underlying etiology of respiratory failure and resultant lung injury has resolved. In this regard, few patients actually *require* invasive mechanical ventilation (IMV) and, although standard criteria are frequently described, the decision to intubate (or not) is ultimately based on clinical judgement. A decision to intubate is often made under certain clinical scenarios. One of these is when NIV is deemed unsafe or ineffective, for example, due to lack of airway protection. Another typical scenario is when the degree of hypoxemia continues to worsen despite the application of high fraction of inspired oxygen and/or PEEP. Finally, a decision to intubate can be made when the work of breathing is perceived to be increased, possibly leading to worsening lung injury. The highest variability in clinical judgement exists in the last two settings. Even though IMV together with strategies targeted to a tighter control of ventilation can lead to an improvement in oxygenation and mitigate the potential risks that excessive work of



Supported by a Vanier Canada Graduate Scholarship (B.L.F.).

DOI: 10.1513/AnnalsATS.202109-1059ED

breathing carries, the exact threshold in which the benefits of invasive ventilation outweigh the accompanied risks is unclear. In this regard, the subjective gestalt of the clinician likely plays a major role in the decision to intubate. Furthermore, given the variability in the estimated efficacy of NIV for AHRF, clinicians might weigh in their own interpretation of the efficacy of NIV in AHRF when making these decisions. In summary, the fundamental problem in defining NIV failure resides in how to discriminate objective criteria and true mechanisms from a decision that is largely based on subjective clinical judgment.

Another important question stemming from the study by Shu and colleagues is, what is the role of identifying early predictors of NIV failure? For example, let us consider a perfect predictive score with excellent discrimination and validity. What would be its direct clinical applicability? A first logical answer is that this would help us identify patients who would benefit from early intubation, avoiding harms associated with continuing NIV. NIV with positive pressure may lead to ventilator-induced lung injury through similar mechanisms as those proposed for IMV, particularly in spontaneously breathing patients (28). The potential benefits or harms of early intubation as a way to control vigorously labored breathing have been extensively discussed (29–32). Furthermore, the evidence surrounding the dilemma of early versus late intubation is characterized by important methodological challenges, which limit its clinical applicability (33, 34). A second answer is whether identifying predictors of failure might lead to clinical interventions that could modify that risk. In this regard, understanding mechanisms of failure and discerning mechanisms from decisions is where the higher clinical value might remain. Understanding the underpinnings for each cause of NIV failure remains key to tailor adequate responses to each scenario, and future research should focus on describing such mechanisms.

In conclusion, the study from Shu and colleagues adds important insights with regard to common criteria present at baseline that may identify patients with a higher risk of intubation. Importantly, the study sets the stage for future research in the field, specifically in the identification of specific mechanisms of failure and clinical thresholds to be used when switching to IMV, that can potentially be translated into better patient outcomes. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

**Acknowledgment:** The authors thank Dr. Federico Angriman for his thoughtful comments on this editorial.

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# Health Inequities and Racial Disparity in Obstructive Sleep Apnea Diagnosis: A Call for Action

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The World Health Organization defines health inequities as the systematic differences in the health status or in the distribution of health resources to different groups. Striving for health equity ultimately means eliminating social determinants, including racial bias, to improve access to good medical care (1). Eighteen years ago, the institute of medicine identified that racial minorities receive lower quality of health care than nonminorities, even when factors such as insurance status and income were considered (2). Racial disparities to health and specifically sleep health are common, prevalent worldwide, and avoidable (3). African Americans with obstructive sleep apnea (OSA), compared with matched White individuals, are often found to have severe disease (4, 5), use treatment with positive airway pressure devices less (depending on their zip code) (6, 7), and are more susceptible to uncontrolled hypertension (8).

In this issue of *AnnalsATS*, Thornton and colleagues (pp. 272–278) investigate the impact of racial disparity on the diagnosis of OSA (9). Their report was derived from a large university-based sleep lab cohort and showed that Black people, especially Black men, have more severe disease than their White counterparts and yet present with standard symptoms of daytime sleepiness or snoring. Black males and females were 5 years younger than their White counterparts and had higher body mass indexes (~5 kg/m$^2$) and higher percentages of hypertension. Apnea severity was also worse; among Black men, mean apnea hypopnea index was 52.4 ± 39.4 events per hour compared with 39.0 ± 28.9 events per hour in White men, 33.4 ± 32.3 events per hour in Black women, and 26.2 ± 23.8 events per hour in White women. Subjective sleepiness as measured by the Epworth Sleepiness Scale score was highest in Black men (12.12 ± 5. 9) followed by Black women (11.2 ± 5), White women (9.8 ± 5.6), and White men (9.4 ± 5.2). Thus, Black males made up the smallest percentage of the cohort but had more disease and it impacts them more severely from a sleepiness standpoint than the other groups, which raises the question, why are these patients not identified sooner?

There are three potential mechanisms leading to this finding, including *1*) limited screening for OSA in Black people at the primary care level; *2*) overlapping symptoms



DOI: 10.1513/AnnalsATS.202108-984ED