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Go with the Flow: Expanding the Definition of Acute Respiratory Distress Syndrome to Include High-Flow Nasal Oxygen

High-flow nasal oxygen (HFNO) delivers heated, humidified oxygen at very high flow rates (20–70 L/min) at concentrations up to 100% through a specialized nasal cannula. HFNO has several physiologic advantages compared with conventional oxygen delivery, including a reduction in dead space, decrease in work of breathing, and provision of low levels of end-expiratory pressure resulting in increased end-expiratory lung volume (1, 2). In addition to physiologic benefits, most patients find HFNO more comfortable than noninvasive ventilation (NIV) with a tight-fitting mask. For these reasons, over the past two decades, uptake of HFNO in the ICU setting as an alternative to conventional oxygen therapy and NIV has increased across a variety of settings, including early management of patients with acute hypoxemic respiratory failure (AHRF) due to acute lung injury. In 2015, the FLORALI (High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure) trial provided reassurance that HFNO is a safe substitute for conventional oxygen delivery or NIV in patients with AHRF and showed a mortality benefit and increase in ventilator-free days for the group treated with HFNO (3).

Originally Published in Press as DOI: 10.1164/rccm.202112-2727ED on January 10, 2022

The onset of the global pandemic of coronavirus disease (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in 2019 has increased the pace for the adoption of HFNO. This rapid acceleration has been driven by several unique challenges engendered by the pandemic, including *1*) massive surges in patients presenting with AHRF requiring high levels of supplemental oxygen; *2*) shortages of ICU beds, ICU staffing, and mechanical ventilators, leading more patients to be managed when possible with alternatives to invasive mechanical ventilation (IMV); *3*) the need to provide high levels of oxygen supplementation with HFNO outside of an ICU setting, which is not as feasible for NIV or IMV; and *4*) the implementation of awake proning for severe COVID-19, which is more feasible with HFNO than NIV. Despite its widespread adoption, there is currently no firm evidence in the population of patients with COVID-19 that HFNO confers benefits in terms of mortality or other clinical outcomes that have been reported in non–COVID-related AHRF, but few randomized controlled trials have been published (4, 5). Nevertheless, the entrenchment of HFNO in the ICU therapeutic armamentarium for AHRF will be one legacy of this pandemic.

As HFNO has been incorporated into the routine management of patients with AHRF, some important implications have arisen for the diagnosis of acute respiratory distress syndrome (ARDS). The Berlin definition of ARDS (6) stipulates that a patient must be receiving positive pressure ventilation with a minimum of 5 cm H_2O of continuous positive airway pressure; for moderate or severe ARDS, invasive mechanical ventilation is required. However, even before the

pandemic, it was clear that some patients who otherwise met the Berlin criteria for ARDS (acute onset, bilateral opacities on chest radiograph, and hypoxemia as measured by Pa_{O_2}/FI_{O_2} ratio) could be managed, at least initially, with HFNO rather than IMV. This observation suggested that the arrival of HFNO as a therapeutic strategy could actually be hindering the timely diagnosis of ARDS and preventing the application of ARDS therapies. This has led several groups (7, 8) to propose that HFNO be added to the definition of ARDS based on the following: *1*) patients with severe hypoxemia who otherwise meet the ARDS definition have the same physiology, biomarkers, and clinical outcomes as ventilated patients, suggesting they fulfill the conceptual model of ARDS proposed in both the AECC and Berlin definitions (9, 10); *2*) the low levels of positive airway pressure provided by HFNO fulfill the requirement for positive end-expiratory pressure (PEEP) specified in the Berlin definition; *3*) this change would allow ARDS to be diagnosed more readily in underresourced areas where access to IMV or NIV is limited, but HFNO is available (11), and; *4*) expansion of the definition would facilitate earlier identification and treatment of patients with ARDS. Indeed, many recent clinical trials have already allowed enrollment of patients who otherwise meet ARDS criteria but are being treated with HFNO. Another group has suggested a more pragmatic modification to define ARDS in COVID-19 pneumonia based solely on the presence of AHRF requiring HFNO, NIV, or IMV (12). However, the potential impact of either change on the overall severity of patients identified has been difficult to define.

In this issue of the *Journal*, Ranieri and colleagues (pp. 431–439) provide new data to help inform this discussion (13). Ranieri and colleagues analyzed outcomes of patients with COVID-19 pneumonia from four Italian studies, including three observational and one interventional study. Patients who met all Berlin ARDS criteria other than IMV who were receiving HFNO ($n = 184$) or NIV ($n = 131$) for at least 12 hours at the time of study enrollment were included. The majority of patients progressed to require IMV (61% in the HFNO and 53% in the NIV group), and 28-day mortality was 19% in the HFNO group and 24% in the NIV group. In the subset of each group who never required IMV, mortality was low regardless of modality (4.2% in HFNO and 1.6% in NIV). The authors conclude that expanding the definition of ARDS to include patients with PF $\leqslant$300 receiving HFNO would include patients with lower mortality. These findings are important, but several caveats need to be considered. First, the patient population was small and highly selected. Second, all patients were cared for under surge conditions, which may affect the generalizability of the results. Third, many patients were cared for outside the ICU, which may have selected for less acutely ill patients. Fourth, low mortality was observed in both HFNO and NIV patients who did not ever require intubation; patients who progressed to require intubation had substantial mortality (29% for HFNO and 45% for NIV), suggesting that earlier diagnosis of ARDS in these patients could provide an important window for early intervention in a group at high risk of poor outcomes.

Where does this leave the global critical care community with regard to the definition of ARDS? A Global Consensus Conference was convened in 2021 to consider whether a change in the definition of ARDS is currently warranted. From a practical standpoint, as HFNO continues to gain traction as a therapy for AHRF, the inclusion of patients requiring HFNO seems a sensible expansion. Given the low level of PEEP provided by HFNO, it would also serve to preserve the intent of the Berlin definition to identify patients with substantial hypoxemia that does not resolve with the application of PEEP. However, the concern that such an expansion would identify patients with less severe disease also has merit, and multicenter, prospective studies in both COVID and non-COVID ARDS will be needed to answer this question. From a therapeutic standpoint, expanding the definition of ARDS to include patients treated with HFNO would facilitate testing and application of new therapies in patients at high risk of poor outcomes. ■

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

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Preemptive Noninvasive Ventilation to Facilitate Weaning from Mechanical Ventilation in Obese Patients at High Risk of Reintubation

Weaning from mechanical ventilation and extubation are critical procedures in mechanically ventilated patients, as weaning failure and reintubation occur in up to 10–30% of cases and are associated with increased mortality (1). Different tools have been proposed to prevent and treat postextubation respiratory failure, but there is a substantial lack of final evidence regarding the optimal tool for the management of patients undergoing scheduled extubation in the ICU.

Although the uncontrolled use of preemptive noninvasive ventilation (NIV) using pressure support ventilation with positive end-expiratory pressure (PEEP) in unselected cohorts of critically ill patients may lead to delayed reintubation and worsen mortality (1), it may be of benefit as a bridge to full spontaneous breathing in hypercapnic patients and in selected cohorts of hypoxemic subjects at high risk of weaning failure (2).

Heated and humidified high-flow nasal cannula (HFNC) appears as the optimal tool to administer oxygen to hypoxemic patients in the weaning phase (3, 4). HFNC allows accurate delivery of the set $F_{I_{O_2}}$, provides a low PEEP level (<5 cm H_2O), and reduces work of breathing by favoring CO_2 clearance from upper airways (5, 6). Preemptive HFNC has been shown to reduce the need for reintubation in a large randomized trial when compared with low-flow oxygen after the extubation of critically ill patients at low risk of weaning failure (7), and seemed as effective as NIV in patients at high risk of weaning failure (8).

These data indicate that, in patients who have high risk of extubation failure, both HFNC and NIV are promising techniques and may finally improve clinical outcomes (9). Further evidence regarding the best balance between these two techniques came from a recently published multicenter clinical trial, in which 641 critically ill patients showing at least one risk factor for extubation failure (i.e., age >65 yr, underlying chronic cardiac or lung disease, 50% of patients were recovering from respiratory failure) were randomly assigned to receive NIV alternating with HFNC or HFNC alone as preemptive treatments after scheduled extubation in the ICU (8). NIV was delivered for sessions of at least 4 hours, with a minimal treatment duration of 12 hours per day in the initial 48 hours, and was applied through a face mask and specific settings: pressure support titrated to obtain an expiratory V_T between 6 and 8 ml/kg of predicted body weight and PEEP ranging between 5 and 10 cm H_2O. Study results showed that the preemptive combined use of NIV and HFNC resulted in a lower rate of reintubation at 7 days and in a lower incidence of postextubation respiratory failure as compared with HFNC alone.

In this issue of the *Journal*, Thille and colleagues (pp. 440–449) report the results of a *post hoc* analysis of the trial, in which intergroup differences in study outcomes were analyzed after classifying patients according to whether they were obese (BMI $\geq$ 30 kg/m^2; 206 patients), overweight (25 kg/m^2 $\leq$ BMI < 30 kg/m^2; 204 patients), or normal/underweight (BMI < 25 kg/m^2; 213 patients) (10). The research question addressing the potential heterogeneity in NIV effects according to different BMI is sound, as obesity significantly interferes with the physiology of respiratory system; this may affect the effect of applied interventions (11, 12).

Study results showed that, in the subgroup of patients who are obese or overweight, the rate of reintubation rate at Day 7 was significantly lower in patients treated with NIV alternating with HFNC than in those who received HFNC alone (7% [15/204] vs. 20% [41/206], with an absolute risk reduction of 13% and a number needed-to-treat of 8). This result was accompanied by significantly lower time in the ICU and 90-day mortality in patients treated with NIV alternating with HFNC.

Conversely, no intergroup difference in study outcomes was found in patients who had BMI <25 kg/m^2.

These results have a robust physiological rationale. Obesity is associated with increased absolute values of pleural pressure, which favors the development of atelectasis; atelectasis yields intrapulmonary shunt and consequent hypoxemia (11), which is the most frequent cause of extubation failure. Atelectasis may also cause reduction in lung and respiratory system compliance, which increases the muscle workload to generate an adequate V_T. PEEP, by counterbalancing pleural pressure, maintains positive transpulmonary pressure, prevents atelectasis due to alveolar collapse, and favors a more homogeneous ventilation (11). Also, airway closure and expiratory flow limitation are magnified in patients who are obese (13, 14). Application of PEEP may reduce work of breathing by preventing airway closure and limiting the isometric muscle workload needed to generate inspiratory flow. This, together with the inspiratory assistance provided by pressure support, may reduce the

Originally Published in Press as DOI: 10.1164/rccm.202111-2649ED on December 15, 2021