studies and the identification of trajectories of respiratory health. These trajectories, however, lack the resolution of data to inform the interplay of disease-specific features, which, as the authors suggest, may be most important for targeted interventions. Unlike the prize of 1714, the multiple data "chronometers" described in the literature, including EPGA, should not be considered part of a competition for truth. Each provides new analytic strategies, reinforcing concepts, and leverage existing data that push us to think in new directions. Most important, these efforts highlight the need for ongoing investment in observational studies of participants at risk for COPD to truly understand COPD evolution. ■

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Nasal High Flow to Modulate Dyspnea in Orally Intubated Weanable Patients

Dyspnea is a prevalent and distressing symptom in critically ill patients, and it is associated with poor outcomes (1). Among patients hospitalized for acute illness, those with a higher amount of dyspnea experience physical and psychological suffering, a higher risk of noninvasive ventilation failure (2), and prolonged duration of invasive mechanical ventilation (3, 4). The presence of dyspnea is also associated with hospital mortality (2, 5) and post-ICU post-traumatic stress disorder occurrence (6, 7). Thus, breathing discomfort should be addressed to minimize both immediate suffering and long-term sequalae when assessing mechanically ventilated patients (1). In addition, any strategy aimed at relieving dyspnea is substantial and represents a research priority in ICU patients (1).

In this issue of the *Journal*, Le Stang and colleagues (pp. 577–586) provide new insight into the clinical benefits of nasal high-flow therapy (NHF) on dyspnea relief assessed by two different endpoints: the Numerical Rating Scale (NRS) and the Mechanical Ventilation Respiratory Distress Observational Scale (8). The authors conducted a prospective physiological study in 20 orally intubated patients undergoing weaning from invasive mechanical ventilation, applying NHF at different flow rates during pressure support ventilation and spontaneous breathing trials (SBTs) (8). It is well known that several physiological benefits that combine the ability to humidify and heat gases with the capacity to provide high flow rates make NHF potentially suitable for patients with hypoxemic and hypercapnic respiratory failure (9). A strength of this work lies in the fact that the application of NHF in orally intubated patients allowed the evaluation of the NHF nasal effects on dyspnea and respiratory drive regardless of its mechanisms of action on the respiratory system (8).

Of note, at baseline, under pressure support ventilation, enrolled patients reported a "moderate intensity" dyspnea (NRS = 5), but they did not present high inspiratory drive and effort, as shown by the median airway occlusion pressure ($P_{0.1}$) of 3 cm H_2O and median negative inspiratory swing of esophageal pressure of 7 cm H_2O, respectively (8). Although a large interindividual variation, 71% of

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the patients under pressure support had a reduction in dyspnea-NRS with NHF at 30 L/min, with no effect on respiratory drive and breathing pattern. In addition, during the SBT, the administration of NHF at 50 L/min was associated with a lower dyspnea-NRS score ($P < 0.01$), a lower $P_{0.1}$ ($P = 0.04$), and a higher esophageal pressure–time product (PTPeso) per breath ($P = 0.05$), whereas inspiratory work and minute ventilation did not change compared with SBT without nasal high flow (8).

Interestingly, no correspondence was found between the two scales used to assess the dyspnea. In fact, no reduction of Mechanical Ventilation Respiratory Distress Observational Scale has been demonstrated with NHF regardless of the trials (8). This is in line with previous evidence demonstrating that dyspnea is difficult to estimate based on observations of physical and behavioral signs, with clinician underestimation of patient's self-reported dyspnea (4). At the same time, in invasively mechanically ventilated patients, several factors (i.e., the presence of the endotracheal tube, the level of sedation, delirium, etc.) can contribute to reducing the ability of patients to communicate or self-assess a symptom, also changing the individual dyspnea perception (1).

This study also reinforces the concept that dyspnea is not necessarily linked to the patient's neural respiratory drive and breathing effort. Several years ago, Veen and colleagues (10) clearly demonstrated that patients with severe asthma, particularly those with frequent exacerbations, had an impaired perception of dyspnea. This phenomenon can be interpreted as resulting from the adaptation to the airway hyperresponsiveness, which leads to raising the threshold degree of dyspnea (10). This example explains clearly that the neurophysiology of dyspnea is complex. In accordance with the uncoupling theory (11), dyspnea occurs in cases of mismatch between the expected results (corollary discharge) and real (afferent) sensory information (1, 11). Inspiratory drive and effort represent the final pathway of breathing, and their dissociation (i.e., high inspiratory drive with low effort or vice versa) described in critically ill patients, especially in cases of acute respiratory distress syndrome, can cause shortness of breath (10). However, unpleasant respiratory sensations can also arise from cognitive and emotional factors through signals from the limbic system (1, 8). In light of these observations, the same author group recently published a paper (12) showing that facial stimulation or musical distraction reduced dyspnea visual analog scale score to a similar extent as NHF in patients receiving mechanical ventilation for more than 48 hours, without affecting the EMG signal or $P_{0.1}$ measures (13). In this study, facial stimulation consisted of blowing cool air toward the patient's face using a bladeless fan (12).

Fan therapy is a nonpharmacological approach able to alleviate breathlessness by trigeminal activation of brain regions related to dyspnea (i.e., insular cortex, anterior cingulate cortex, and amygdala). Different from fan therapy, NHF delivers humidified and heated air flows in the nasal cavity. However, the mechanism through which NHF can improve dyspnea in intubated patients remains unclear. Although fascinating, the hypothesis that NHF can modulate dyspnea and respiratory drive through the proximity and anatomical relationship between the olfactory bulbar and the limbic system needs further investigation (8, 13, 14).

This study was intended to be a proof of concept to explore a novel approach of dyspnea and respiratory drive modulation in intubated patients. The results are too preliminary to be translated into clinical practice and pose questions about the future potential applicability in low-resource settings. However, even though parts of the hypothesis reported are speculative, the authors offer interesting options for further development and research. ■

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What Can We Learn from Differences in Hospitals' Sepsis Care?

Sepsis remains a major cause of mortality and disability the world over. Death certificate analyses suggest that sepsis accounts for at least one in five deaths worldwide (1). There is considerable variation, however, in sepsis incidence and mortality between regions. Age-standardized sepsis mortality rate estimates are almost 20 times higher in sub-Saharan Africa than in Western Europe. There is also substantial variability within regions: Age-standardized mortality rates vary fourfold across Europe, ranging from 18.0 to 81.9 deaths per 100,000 persons (Finland and Moldova, respectively) (1).

The considerable variability in sepsis mortality rates within and between regions begs the question, "Why?" Is the variability due to differences in patient factors (comorbidities, infection types, pathogens, etc.), infrastructure (distance to hospital, hospital services, etc.), or care factors (sepsis screening and recognition, time to antibiotics, fluid resuscitation, etc.)? A comprehensive survey on sepsis care in over 1,000 hospitals, mainly in Europe, published in this issue of the *Journal* (pp. 587–599) provides welcome insight into differences in sepsis infrastructure and care protocols within Europe (2).

The European Sepsis Care Survey was a voluntary survey organized by the European Sepsis Alliance to assess hospitals' adoption of Surviving Sepsis Campaign guideline recommendations and their infrastructure to support sepsis care. The survey was conducted between August 2021 and June 2022. Responses were received from 1,023 hospitals, 82% of which were in Europe. The authors identified substantial differences between hospitals in their processes of care, infrastructure, and data monitoring.

Key findings included the following. Less than one-third of surveyed hospitals had formal sepsis quality improvement programs. Almost 50% of emergency departments were not routinely using sepsis screening tools such as systemic inflammatory response syndrome criteria, quick Sequential Organ Failure Assessment criteria, or early warning scores. Only 57% of emergency departments had implemented standardized management bundles for patients with sepsis. Less than 5% of hospitals were providing targeted funding for a sepsis quality improvement program or specialized sepsis staff.

Similar gaps were apparent in hospitals' infrastructure for timely sepsis diagnosis and management. About 90% of hospitals had round-the-clock access to computed tomography and magnetic resonance imaging, and 87% could access surgical services for source control at any time. Less than one-third of hospitals, however, had access to interventional radiology for source control whenever needed, and less than 10% of hospitals provided microbiology services such as blood culture inoculation, identification of pathogens, and result reporting outside of standard working hours. About three-fourths of hospitals provided local guidelines or standard operating procedures to guide antibiotic choices for patients with sepsis, but only two-thirds of hospitals had antimicrobial stewardship teams, and less than one-third had regular access to infectious disease specialists for consultation.

Likewise, most hospitals conducted very limited monitoring of sepsis rates, outcomes, and processes of care. Only about half monitored sepsis incidence and mortality. One-fifth monitored time to antibiotic administration. Less than one-fifth measured sepsis bundle compliance overall.

The considerable variability and low overall implementation of sepsis protocols, support services, and monitoring documented by the European Sepsis Care Survey is concerning. Sepsis is a leading cause of death worldwide that merits dedicated attention, resources, and expertise. The challenge all hospitals face, however, is determining how best to allocate their limited resources to maximize patient benefit. The European Sepsis Care Survey assessed a very broad range of potential screening strategies, care processes, and support infrastructure that may improve sepsis outcomes. There are very limited data, however, on which of these are most impactful and thus ought to be prioritized by hospitals working to improve their sepsis care and outcomes.

The U.S. experience with sepsis quality improvement is perhaps informative in this regard. Whereas barely one-third of hospitals in the European Sepsis Care Survey had sepsis quality improvement programs and only about half were actively screening patients for sepsis, more than three-fourths of U.S. hospitals have sepsis quality improvement programs, and more than 90% screen patients for sepsis (3). This large difference is almost certainly attributable to U.S. state and federal initiatives that require hospitals to implement sepsis screening and treatment protocols and/or report their compliance with sepsis management bundles. These initiatives have raised sepsis consciousness among providers, administrators, and members of the public and are helping to ensure that all hospitals develop formal pathways to improve sepsis recognition and initial care.

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