

Air Hunger and Psychological Trauma in Ventilated COVID-19 Patients: An Urgent Problem

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An unprecedented number of people will experience mechanical ventilation in the next few months due to the COVID-19 pandemic. Our clear mission is to sustain these patients while they mount an immune defense to the virus, and to do minimum harm in the process. A key therapeutic strategy will be lung protective ventilation, an approach that entails low tidal volumes and permissive hypercapnia, for treatment of acute respiratory distress syndrome (ARDS) caused by the virus. Unfortunately, this is also the recipe for “air hunger” – the most uncomfortable form of dyspnea.¹

Recent reports of patients with severe COVID-19 infections admitted to intensive care units (ICUs) in Italy², Seattle³, New York City⁴, and our own ICUs in Boston⁵, help estimate the problem: 75-88% of these patients were mechanically ventilated, with median duration of mechanical ventilation of 10 and 16 days in the Seattle and Boston cohorts, respectively. In these same two cohorts, prior to intubation and mechanical intubation, dyspnea was a very common presenting symptom in severe COVID-19 infection, present in on presentation in 88% and 91% of patients, respectively. With the likelihood that hundreds of thousands of dyspneic patients will require low tidal volume mechanical ventilation around the world, we are concerned about the potential for mass psychological trauma in the survivors induced by untreated air hunger during this pandemic.

The problem is not intractable, however. Physicians who are treating ARDS due to COVID-19, some of whom may not be accustomed to treating patients with respiratory failure, must first be aware of the problem and then consider means by which air hunger can be ameliorated.

Anyone who has held his or her breath for an extended period knows the sensation of air hunger, the predominant uncomfortable symptom reported by ventilated patients.⁶ While a voluntary breath hold can be ended instantly, a mechanically ventilated patient does not have that option. Prolonged air hunger evokes fear and anxiety, so much so that involuntary air hunger has been used as a very effective form of torture (e.g. waterboarding).⁷ Among ICU survivors, the experience of air hunger is associated with post-traumatic stress disorder (PTSD).⁶

Air hunger is evoked by an increase in medullary respiratory drive projected to the cerebral cortex (corollary drive) and is ameliorated by tidal inflation of the lungs, sensed by vagal pulmonary stretch receptors.⁶ Low-volume lung-protective ventilation decreases tidal stretch receptor input and often increases respiratory drive (via elevated PCO_2). We can infer from reported driving pressure and compliance measurements in the Seattle and Boston cohorts that tidal volumes were small (less than 400mL on days 1 and 2) to minimize lung damage. Our local experience is that COVID-19 patients can present with elevated respiratory drive and are often intubated and placed on mechanical ventilation in some degree of respiratory distress. This is consistent with a report from Wuhan⁸ that showed hyperpnea prior to intubation (median PaCO_2 34 Torr in 138 hospitalized patients) and many patients in the Seattle cohort were tachypneic on arrival. Median PaO_2 in the Wuhan cohort was 68 mmHg – insufficient hypoxia to generate significant hyperpnea or air hunger. Thus, the excess drive may arise from lung afferent nerves stimulated by inflamed or collapsed lung units and contributes to the sensation of dyspnea, which was present in 21 of 24 the Seattle ICU patients on initial presentation.

Unfortunately, it is very difficult to estimate a patient's dyspnea using observed signs – physicians and nurses consistently and substantially underestimate dyspnea compared to patient report.⁹ Air hunger is not due to increased work of breathing, so we should not expect that dyspnea will be relieved by assuming work of breathing with a ventilator, particularly when tidal volumes are set to be low. Neuromuscular blockade is often used in ARDS to control patient-ventilator interaction, and there is a persistent mistaken notion that paralysis reduces dyspnea (a notion based on now-disproven theories that were popular several decades ago); we now know that neuromuscular blockade does not diminish air hunger.⁶ In the Seattle cohort, neuromuscular blockade was used in 39% of mechanically ventilated patients. Paralysis exacerbates the inherent challenges to managing dyspnea by eliminating most observable signs of the symptom.

There is, however, an easily accessible remedy with which most physicians are familiar: opiates. Opiates are the most reliable agent for symptomatic relief of air hunger – they seem to act both through depression of ventilatory drive and ascending perceptual pathways, as they do with pain.¹⁰ In opiate-naïve healthy subjects, 5mg of intravenous morphine provided profound relief of experimentally induced air hunger, and studies of opiate-relief of clinical dyspnea using even low doses of opioids similarly show relief from breathlessness.^{10,11} Although the anti-dyspnea effect of opioids is generally well known, patients with ARDS in the ALVEOLI trial were given opioids as part of their initial sedation strategy only about 60% of the time,¹² a rate similar to the 55% seen in a small meta-analysis¹³ of ARDS studies, suggesting many patients with ARDS are not receiving the best known therapy to relieve dyspnea.

Other common pharmacological interventions are likely to have less of an effect.

Evidence shows that benzodiazepines are not effective for dyspnea¹⁴ and a mounting evidence base suggests they exacerbate psychological trauma.¹⁵ Propofol is commonly used to sedate ventilated patients, but there are no data on its effectiveness in relieving dyspnea. In small doses, propofol has little effect on respiratory drive and may even exacerbate pain¹⁶; however, high doses of propofol cause ventilatory depression and may relieve air hunger.¹⁷

During this crisis, we urge physicians providing critical care to attend to the possibility of extreme air hunger in ventilated COVID-19 patients with ARDS, and to consider the known pharmacologic benefits of opiates in their management.

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