Oxygenation Indices in Noninvasive Ventilation: Could They Predict Mortality in COVID-19?

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The best way to predict the future is to study the past, or prognosticate
—Robert Kiyosaki

Coronavirus disease-2019 (COVID-19) has plagued our lives and healthcare system since March, 2020. As of this day, the disease has already claimed close to 39,80,000 lives around the world and 4,00,000 lives in India alone since 2020. Hypoxemia in COVID-19 is attributed primarily to ventilation perfusion mismatch and intrapulmonary shunting, thereby causing an elevated alveolar–arterial gradient (A–a gradient). Another unique feature of COVID-19 is that the hypoxemia maybe disproportionate to the abnormalities in the lung compliance.

As clinicians, the simplest way to identify patient’s oxygenation status is by measuring the oxygen saturation (SpO2) with pulse oximetry. However, this must be correlated with the FiO2 at which the readings are taken. The estimation of FiO2 especially when the patient is not intubated or breathing at room air is exceedingly difficult. It has been seen that patients on nasal prongs with 2 L of oxygen could have a FiO2 ranging from 24 to 35%. Arterial blood gases give us a better picture of patients oxygenation and ventilation status with parameters of PaO2, PaCO2, and HCO3. Low PaO2 remains to be the key parameter to measure a patient’s oxygenation. Oxygen tension–based indices are usually used at the bedside by clinicians to assess the patient’s response to the treatment and to quantify the severity of lung involvement. The popular indices used include the A–a gradient, PaO2/FiO2 ratio or the Horowitz index, a/A ratio, and oxygenation index.

The A–a gradient, first described by Mellemgard, is based on the alveolar gas equation and gives a good insight into the differential diagnosis of hypoxemia. An increased A–a gradient often points to various pathologies involving the lung and right-to-left shunts. One of its main criticisms is that it is highly influenced by the FiO2 and shunt. The a/A ratio is on the other hand has been shown to give a better idea of the cause of oxygenation failure, with less influence by the fraction of inspired oxygen. Although this has been critiqued and shown to be true only in the case of large shunts.

The PaO2/FiO2 ratio is simply the ratio of the alveolar oxygen tension by the fraction of inspired oxygen. PaO2/FiO2 ratio is common parlance during intensive care unit (ICU) rounds or handovers, much so during the recent pandemic. The PaO2/FiO2 ratio is an integral part of the acute respiratory distress syndrome (ARDS) definitions, both the American-European consensus conference (AECC) and Berlin’s definition. Based on the PaO2/FiO2 ratios, the Berlin’s criteria classifies ARDS into mild, moderate, and severe disease with an estimated mortality of 27, 32, and 45%, respectively. This ratio has its share of limitations in that it gives no clue to the cause of hypoxemia or does not take the barometric pressure into consideration. Recently, Tobin et al. referred to the PaO2/FiO2 ratio as “the mismeasurement of all things oxygen” with regards to COVID-19. While PaO2/FiO2 ratio may have its share of fallacies, they carry the advantage of easy calculation at the bedside and widespread use. The respiratory index is not as frequently used as the other indices and has a similar clinical significance as that of the a/A ratio. The A–a gradient and PaO2/FiO2 ratio are also important variables in commonly used ICU scoring systems, like APACHE II and Sequential Organ Failure Assessment (SOFA). The use of A–a gradient has been shown to predict mortality in other clinical settings as well. In pediatric patients undergoing bone marrow transplantation, oxygenation index and A–a gradient were shown to be good predictors of mortality. The A–a gradient has also shown to be a predictor in HIV patients who developed Pneumocystis pneumonia as well as an indication to initiate steroid therapy in these patients. A pilot study by Gabrielli et al showed that an elevated A–a gradient did have a significant correlation with ICU admission in COVID-19, but not with mortality.

Invasive ventilation remains to be the cornerstone for the management of patients with severe ARDS. With COVID-19, clinicians over the world have opted for noninvasive strategies, like noninvasive ventilation (NIV), continuous positive airway pressure, or high-flow nasal oxygen therapy, at initial presentation as compared to invasive ventilation at the get-go. These noninvasive strategies have also been advocated in the surviving sepsis guidelines for COVID-19. The role and timing of intubation in COVID-19 patients are still highly debated. A recently published editorial even went on to state that “liberal use of invasive ventilation has been described as the surest way of increasing mortality.” One cannot also overlook the shortage of ventilators that occurred during the pandemic. Particularly in the devastating second wave of the COVID-19 pandemic, there was a heightened use of noninvasive ventilatory strategies owing to the shortage of ICU beds with ventilators across the country. Various
investigators and clinicians have tried to study the predictors of mortality in COVID-19. These included age >50 years, male sex, presence of comorbidities, and higher inflammatory markers, like D-dimer, interleukin-6, C-reactive protein, cardiac troponins, and SpO\textsubscript{2}/FiO\textsubscript{2} <400.\textsuperscript{12,13} However, it is equally important to identify similar predictors in patients initiated on NIV.

In this month’s issue, Gupta et al. have evaluated the utility of these oxygen tension indices to predict mortality in patients with COVID-19 receiving NIV, particularly the A–a gradient.\textsuperscript{14} The differences in these indices, which included the PaO\textsubscript{2}/FiO\textsubscript{2} ratio, A–a gradient, respiratory index, and a/A ratio, were significant among the COVID-19 survivors vs the nonsurvivors in this study. Optimal criteria for ABG parameters, like PaO\textsubscript{2}, PaCO\textsubscript{2}, and bicarbonate levels to predict mortality were also identified, although with varying degrees of sensitivity and specificity.

Simplifying predictors of mortality due to COVID-19 remains to be a challenge. While these oxygenation tension indices are fraught with fallacies, one cannot deny their simplicity to use and easy to calculate at the bedside. The use of these indices in combination with other measurable respiratory parameters and clinicopathological criteria would be needed to build a more robust model for prognostication for COVID-19.

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