EDITORIALS

Basing Respiratory Management of COVID-19 on Physiological Principles

The dominant respiratory feature of coronavirus disease (COVID-19) is arterial hypoxemia greatly exceeding abnormalities in pulmonary mechanics (decreased compliance) (1–3). Many patients are intubated and placed on mechanical ventilation early in their course. Projections on usage of ventilators has led to fears that insufficient machines will be available and even to proposals for using a single machine to ventilate four patients.

The coronavirus crisis poses challenges for staffing, equipment, and resources, but it also imposes cognitive challenges for physicians at the bedside. It is vital that caregivers base clinical decisions on sound scientific knowledge to gain the greatest value from available resources (4).

Patient oxygenation is evaluated initially using a pulse oximeter. Oxygen saturation as measured by pulse oximetry (Sp_{O_2}) can differ from true Sa_{O_2} (measured with a CO-oximeter) by as much as ±4% (5). Interpretation of readings of Sp_{O_2} above 90% becomes especially challenging because of the sigmoid shape of the oxygen dissociation curve. Given the flatness of the upper oxygen dissociation curve, a pulse oximetry reading of 95% can signify an arterial oxygen tension (Pa_{O_2}) anywhere between 60 and 200 mm Hg (6, 7)—values that carry extremely different connotations for management of a patient receiving a high concentration of oxygen.

Difficulties in interpreting arterial oxygenation are compounded if supplemental oxygen has been instituted before a pulmonologist or intensivist first sees a patient (the usual scenario with COVID-19). Assessment of gas exchange requires knowledge of fractional inspired oxygen tension ($F_{I_{O_2}}$); unless the patient is breathing room air, this is not knowable in a nonintubated patient. With a nasal cannula set at 2 L/min, $F_{I_{O_2}}$ ranges anywhere between 24% and 35% (8).

Arterial blood gases yield a more precise measure of gas exchange. With knowledge of Pa_{O_2}, Pa_{CO_2}, and $F_{I_{O_2}}$, the alveolar-to-arterial oxygen gradient can be rapidly calculated. The alveolar-to-arterial oxygen gradient enables more precise evaluation of the pathophysiological basis of hypoxemia than more widely used $Pa_{O_2}/F_{I_{O_2}}$, because this ratio may reflect changes in P_{O_2}, $F_{I_{O_2}}$, or both.

Hypoxemia accompanied by a normal alveolar-to-arterial oxygen gradient and increase in Pa_{CO_2} signifies hypoventilation. Hypoventilation is uncommon with COVID-19.

Instead, hypoxemia with COVID-19 is usually accompanied by an increased alveolar-to-arterial oxygen gradient, signifying

either ventilation–perfusion mismatch or intrapulmonary shunting (9). (Diffusion problems mainly cause hypoxemia at high altitude.) If a patient's Pa_{O_2} increases with supplemental oxygen, this signifies the presence of ventilation–perfusion mismatch. A satisfactory degree of arterial oxygenation can be sustained in these patients without recourse to intubation and mechanical ventilation. If a patient's Pa_{O_2} does not increase with supplemental oxygen, this signifies the presence of an intrapulmonary shunt; such patients are more likely to progress to earlier invasive ventilator assistance.

Circular thinking is especially dangerous when managing patients with coronavirus. After a patient starts on a therapy, it is often stated that the patient is "requiring" the said therapy. Physicians commonly state that "a patient's oxygen requirements are going up" without making any attempt to measure oxygen consumption; it would be more accurate to simply say the patient's level of supplemental oxygen has been increased. Reports on COVID-19 are also articulated as "patients requiring mechanical ventilation" (1–3). Only a small proportion of patients—largely those in cardiac arrest— "require" mechanical ventilation. In most instances, mechanical ventilation is instituted preemptively out of fear of an impending catastrophe. These patients are receiving mechanical ventilation, and it is impossible to prove that they "required" it when first implemented.

The decision to institute invasive mechanical ventilation (involving an endotracheal tube) is based on physician judgment— clinical gestalt influenced by oxygen saturation, dyspnea, respiratory rate, chest radiograph, and other factors (10). Many patients with COVID-19 are intubated because of hypoxemia; yet, they exhibit little dyspnea or distress. Humans do not typically experience dyspnea until Pa_{O_2} falls to 60 mm Hg (or much lower) (11). I was once a volunteer in an experiment probing the effect of hypoxemia on breathing pattern (12); my pulse oximeter displayed a saturation of 80% for over 1 hour, and I was not able to sense differences between saturations of 80% and 90% (and above). When assessing dyspnea, it is imperative to ask open-ended questions. Leading questions, with the goal of seeking endorsement, can be treacherous (4).

Tachypnea in isolation should rarely constitute the primary reason to intubate; yet, it commonly does (10). Tachypnea is the expected response to lung inflammation that produces stimulation of irritant, stretch, and J receptors (11). Respiratory rates of 25–35 breaths per minute should not be viewed as *ipso facto* (knee jerk) justification for intubation, but rather the expected physiological response to lung inflammation. It is incorrect to regard tachypnea as a sign of increased work of breathing; instead, work is determined by magnitude of pleural pressure swings and tidal volume (9). Palpation of the sternomastoid muscle, and detection

of phasic (not tonic) contraction, is the most direct sign on physical examination of increased work of breathing (4).

Pulmonary infiltrates are commonly seen with COVID-19. Infiltrates on their own are not an indication for mechanical ventilation. Across four decades, I have been seeing patients with extensive pulmonary infiltrates managed with supplemental oxygen. It is only when pulmonary infiltrates are accompanied by severely abnormal gas exchange or increased work of breathing that intubation becomes necessary.

There is a fear that without mechanical ventilation, COVID-19 will produce organ impairment. Evidence of end-organ damage is difficult to demonstrate in patients with Pa_{O_2} above 40 mm Hg (equivalent to oxygen saturation of ~75%) (10). The amount of oxygen delivered to the tissues is the product of arterial oxygen content and cardiac output. In patients with decreased oxygen delivery, oxygen extraction initially increases and oxygen consumption remains normal (13). When oxygen delivery decreases below a critical threshold, this extraction mechanism is no longer sufficient, and total body oxygen consumption decreases proportionally; metabolism changes from aerobic to anaerobic pathways, and vital organ function becomes impaired. This critical threshold does not arise in critically ill patients until oxygen delivery decreases to <25% of the normal value (14).

Once a patient is placed on a ventilator, the key challenge is to avoid complications (15). Mechanical ventilation (in and of itself) does not produce lung healing; it merely keeps patients alive until their own biological mechanisms are able to outwit the coronavirus. The best way to minimize ventilator-associated complications is to avoid intubation unless it is absolutely necessary (16, 17). The surest way to increase COVID-19 mortality is liberal use of intubation and mechanical ventilation.

Within 24 hours of instituting mechanical ventilation, physicians need to consciously evaluate patients for weanability (16, 17). This step is especially important during the COVID-19 pandemic to free up a ventilator for the next patient. Deliberate use of physiological measurements—weaning predictors, such as frequency/V_T ratio (18)—alerts a physician that a patient is likely to succeed in weaning before the physician would otherwise think. These tests achieve their greatest impact if performed when a physician believes that the patient is not yet ready for weaning. Once a patient is ready for a trial of weaning, the most efficient method is to employ a T-tube circuit (19); flow-by (with positive end-expiratory pressure at zero and pressure support at zero) is equally efficient while avoiding environmental contamination. Patients with COVID-19 exhibit severe respiratory failure and differ from the easy-to-wean patients in recent randomized controlled trials.

Never before in 45 years of active practice have I witnessed physicians coping with inadequate medical resources—specifically a shortage of ventilators. Given this situation, it is pivotal that caregivers have the requisite knowledge to interpret arterial oxygenation scientifically, know when to institute mechanical ventilation, and equally know how to remove the ventilator expeditiously to make it available for the next patient. ∎

Martin J. Tobin, M.D.
Division of Pulmonary and Critical Care Medicine
Hines Veterans Affairs Hospital and Loyola University of Chicago Stritch
  School of Medicine
Hines, Illinois

References

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* [online ahead of print] 24 Feb 2020; DOI: 10.1016/S2213-2600(20)30079-5. [Published erratum appears in *Lancet Respir Med* 8:e26.]
2. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al*. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* [online ahead of print] 30 Mar 2020; DOI: 10.1056/NEJMoa2004500.
3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al*.; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* [online ahead of print] 6 Apr 2020; DOI: 10.1001/jama.2020.5394.
4. Tobin MJ. Why physiology is critical to the practice of medicine: a 40-year personal perspective. *Clin Chest Med* 2019;40:243–257.
5. Tobin MJ. Respiratory monitoring. *JAMA* 1990;264:244–251.
6. Jubran A. Pulse oximetry. In: Tobin MJ, editor. *Principles and practice of intensive care monitoring*. New York: McGraw-Hill, Inc.; 1998. pp. 261–287.
7. Severinghaus JW. Simple, accurate equations for human blood O_2 dissociation computations. *J Appl Physiol Respir Environ Exerc Physiol* 1979;46:599–602.
8. Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability of inspired oxygen concentration with nasal cannulas. *Thorax* 1992;47:609–611.
9. Tobin MJ, Laghi F, Jubran A. Ventilatory failure, ventilator support, and ventilator weaning. *Compr Physiol* 2012;2:2871–2921.
10. Laghi F, Tobin MJ. Indications for mechanical ventilation. In: Tobin MJ, editor. *Principles and practice of mechanical ventilation*, 3rd ed. New York: McGraw-Hill, Inc.; 2013. pp. 129–162.
11. Tobin MJ, Gardner WN. Monitoring of the control of ventilation. In: Tobin MJ, editor. *Principles and practice of intensive care monitoring*. New York: McGraw-Hill, Inc.; 1998. pp. 415–464.
12. Jubran A, Tobin MJ. Effect of isocapnic hypoxia on variational activity of breathing. *Am J Respir Crit Care Med* 2000;162:1202–1209.
13. Chittock DR, Ronco JJ, Russell JA. Oxygen transport and oxygen consumption. In: Tobin MJ, editor. *Principles and practice of intensive care monitoring*. New York: McGraw-Hill, Inc.; 1998. pp. 317–343.
14. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, *et al*. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993; 270:1724–1730.
15. Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS: respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;196:822–833.
16. Tobin MJ. Mechanical ventilation. *N Engl J Med* 1994;330:1056–1061.
17. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001;344: 1986–1996.
18. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324:1445–1450.
19. Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdú I, *et al*.; Spanish Lung Failure Collaborative Group. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332:345–350.