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 (FI_{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, FI_{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 FI_{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}/FI_{O_2}, because this ratio may reflect changes in P_{O_2}, FI_{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

Originally Published in Press as DOI: 10.1164/rccm.202004-1076ED on April 13, 2020

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. ■

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

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.

Basing Respiratory Management of Coronavirus on Physiological Principles

Martin J. Tobin MD,

Division of Pulmonary and Critical Care Medicine,

Hines Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine,

Hines, Illinois 60141

(E-mail address: mtobin2@lumc.edu; Telephone: 708-202-2705)

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

The dominant respiratory feature of severe coronavirus disease 2019 (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 employing 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 in order to gain the greatest value from available resources.[4]

Patient oxygenation is evaluated initially using a pulse oximeter. Oximetry estimated saturation (SpO2) can differ from true arterial oxygen saturation (SaO2, measured with a co-oximeter) by as much as ± 4%.[5] Interpretation of SpO2 readings 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 (PaO2) anywhere between 60 and 200 mmHg[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 (usual scenario with Covid-19). Assessment of gas exchange requires knowledge of fractional inspired oxygen concentration (F_IO_2); unless the patient is breathing room air, this is not knowable in a non-intubated patient. With a nasal cannula set at 2 L/minute, F_IO_2 ranges anywhere between 24% and 35%.[8]

Arterial blood gases yield a more precise measure of gas exchange. With knowledge of PaO_2, $PaCO_2$ and F_IO_2, the alveolar-to-arterial oxygen gradient can be rapidly calculated. Alveolar-to-

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

arterial oxygen gradient enables more precise evaluation of the pathophysiological basis of hypoxemia than more widely used PaO_2/F_IO_2, because this ratio may reflect changes in PO_2, F_IO_2, or both.

Hypoxemia accompanied by a normal alveolar-to-arterial oxygen gradient and increase in $PaCO_2$ 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 intra-pulmonary shunting.[9] (Diffusion problems mainly cause hypoxemia at high altitude.) If a patient's PaO_2 increases with supplemental oxygen, this signifies the presence of ventilation-perfusion mismatch. A satisfactory level of arterial oxygenation can be sustained in these patients without recourse to intubation and mechanical ventilation. If a patient's PaO_2 does not increase with supplemental oxygen, this signifies the presence of an intra-pulmonary 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 a cardiac arrest situation—"require" mechanical ventilation. In most instances, mechanical ventilation is instituted preemptively out of fear of an impending catastrophe. These patients are

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

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 x-ray, and other factors.[10] Many patients with Covid-19 are intubated because of hypoxemia—yet exhibit little dyspnea or distress. Humans do not typically experience dyspnea until PaO_2 falls to 60 mmHg (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 an hour and I was not able to sense differences between saturations of 80% versus 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 to 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

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

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 PaO_2 above 40 mmHg (equivalent to oxygen saturation of approximately 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 less than 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 in order to free up a ventilator for the next patient. Deliberate use of physiological measurements—weaning predictors, such as frequency-to-tidal volume ratio[18]—alerts a physician that a patient is likely to succeed in weaning before the physician would otherwise think. These tests achieve their

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

greatest impact if performed when a physician thinks 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 PEEP 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 control 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.

Main Text Word Count: *1252 words*

Conflict of interest: MJT receives royalties for two books on critical care published by McGraw-Hill, Inc., New York.

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

References

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. 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. 2020 Feb 24. pii: S2213-2600(20)30079-5. doi: 10.1016/S2213-2600(20)30079-5. [Epub ahead of print]

2. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, Kritek PA, West TE, Luks A, Gerbino A, Dale CR, Goldman JD, O'Mahony S, Mikacenic C. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med. 2020 Mar 30. doi: 10.1056/NEJMoa2004500. [Epub ahead of print]

3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; 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. 2020 Apr 6. doi: 10.1001/jama.2020.5394. [Epub ahead of print]

4. Tobin MJ. Why physiology is critical to the practice of medicine: a 40-year personal perspective. Clinics in Chest Medicine 2019 Jun;40(2):243-257.

5. Tobin MJ. Respiratory monitoring. JAMA. 1990 Jul 11;264(2):244-51.

6. Jubran A. Pulse oximetry. In: Tobin MJ (ed). Principles and Practice of Intensive Care Monitoring. McGraw-Hill, Inc. New York, 1998, p 261-287.

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

7. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol 1979;46:599-602. (revisions 1999, 2002, 2007).

8. Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability of inspired oxygen concentration with nasal cannulas. Thorax. 1992 Aug;47(8):609–611.

9. Tobin MJ, Laghi F, Jubran A. Ventilatory failure, ventilator support and ventilator weaning. Comprehensive Physiology (Handbook of Physiology, American Physiological Society). 2012;2:2871-2921.

10. Laghi F, Tobin MJ. Indications for mechanical ventilation. In: Tobin MJ (ed). Principles and Practice of Mechanical Ventilation, Third edition. McGraw-Hill Inc., New York, 2012, p129-162.

11. Tobin MJ, Gardner WN. Monitoring of the control of ventilation. In: Tobin MJ (ed). Principles and Practice of Intensive Care Monitoring. McGraw-Hill, Inc. New York, 1998, p 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 (ed). Principles and Practice of Intensive Care Monitoring. McGraw-Hill, Inc. New York, 1998, p 317-343.

14. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 1993;270(14):1724-30.

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

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 Oct 1;196(7):822-833.

16. Tobin MJ. Mechanical ventilation. N Engl J Med. 1994 Apr 14;330(15):1056-61.

17. Tobin MJ. Advances in mechanical ventilation. N Engl J Med. 2001 Jun 28;344(26):1986-96.

18. Yang K, 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, et al. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med. 1995;332:345-350.

AJRCCM Articles in Press. Published April 13, 2020 as 10.1164/rccm.202004-1076ED

Reply to: On Happy Hypoxia and on Sadly Ignored Acute Vascular Distress Syndrome in COVID-19 Patients

Martin J. Tobin MD, Franco Laghi, MD, Amal Jubran, MD

Division of Pulmonary and Critical Care Medicine,

Hines Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine,

Hines, Illinois 60141

Corresponding author:

Martin J Tobin; Division of Pulmonary and Critical Care Medicine

Edward Hines Jr. VA Hospital, 111N; 5000 South 5th Avenue; Hines, Illinois 60141

E-mail addresss: mtobin2@lumc.edu

Funding Source: National Institute of Nursing Research (RO1-NR016055) and Merit Review Award, Veterans Administration Research (1 I01 RX002803-01A1)

Words in body of Letter= 583

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202007-2940LE

To the Editor:

We thank Dr. Jounieaux and colleagues for their comments on our *Perspective* (1).

They raise several points and are especially emphatic about the importance of intrapulmonary shunt in the pathophysiology of COVID-19. Observing hypoxemia in a patient with a viral respiratory tract infection—whether associated with florid or feeble infiltrates—is not a surprise. We did not discuss the mechanisms of hypoxemia in our *Perspective* because one of us had addressed this topic in a recent *Editorial* (2).

The focus of our *Perspective* was the lack of dyspnea in patients with profound hypoxemia (such as PaO_2 of 37 mmHg in our patient MD) (1). In their 2002 study, Jounieaux et al (3) reported that $PaCO_2$ between 29.3 and 34.1 mmHg ablated the ventilatory response to hypoxia. In reality, the threshold is higher: response to hypoxia is absent at $PaCO_2$ of 39 mmHg (4). Thus, a patient with a PaO_2 of 37 mmHg (equivalent to oxygen saturation of 71%) would not be expected to complain of dyspnea if $PaCO_2$ were 39 mmHg (or lower) (1).

Jounieaux and colleagues aver that we deem problems with pulse oximetry as the major explanation for happy hypoxia. We never said that. Physicians recognize the pulse oximetry is remarkably accurate for saturations of 85% to 100%, but many are not aware that pulse oximetry commonly displays falsely low readings—by 10% or more—at saturations less than 80% (1). Given that pulse oximetry is the first tool used to evaluate patients with suspected hypoxemia, this inbuilt tendency to exaggerate the severity of hypoxemia is one factor that may have perplexed some physicians evaluating COVID-19 patients. If a pulse oximeter is displaying a low saturation, it is important to obtain an arterial blood gas whenever possible.

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202007-2940LE

In referring to Figure 1 in our *Perspective* (plot of the ventilatory response to hypoxia), Jounieaux et al claim that low levels of PaO_2 will induce minute ventilations above 20 l/min. That will happen at PO_2 of ~51 mmHg in a normocapnic person (1). If $PaCO_2$ is less than 40 mmHg, minute ventilation will remain unchanged despite profound hypoxia (4).

Jounieaux et al assert that minute ventilation higher than 20 l/min instigates accessory muscle recruitment. In a classic study, Campbell demonstrated that sternomastoid activity (during carbon dioxide rebreathing) did not commence until minute ventilations reached 41 to 105 l/min (5).

COVID-19 has raised many challenges—political, sociological, biological and clinical—but coinage of a new label (AVDS) is unlikely to solve these problems. While intrapulmonary shunt contributes to hypoxia in some COVID-19 patients, shunt does not determine how the respiratory centers respond to hypoxia—and whether a patient complains of dyspnea.

Our *Perspective* was written to provide understanding to physicians (quoted in newspaper articles) who express bewilderment as to the mechanism of happy hypoxia in COVID-19 patients (1). We listed several likely contributors: physiological variables that impact operations of the respiratory control system, fever in producing a rightward shift in the oxygen-dissociation curve, unreliability of pulse oximetry at saturations below 80%, and varying interpretations (among clinicians) as to what the word hypoxemia means (1).

We are concerned that befuddled or ruffled physicians might take actions that negatively impact patient care—such as inserting an endotracheal tube (for mechanical ventilation) in patients not exhibiting an increase in work of breathing and who display oxygen saturations that are low but far from being a threat to life (1,6). We are hopeful that clinical decisions based on a scientific

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202007-2940LE

understanding of biological processes operating beneath a patient's skin result in more rational care and are less likely to cause harm.

Conflict of interest: MJT receives royalties for two books on critical care published by McGraw-Hill, Inc., New York.

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202007-2940LE

References

1. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia is Baffling to Physicians. *Am J Respir Crit Care Med* 2020;202(3):356-360.

2. Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. *Am J Respir Crit Care Med*. 2020; 201:1319-1320.

3. Jounieaux V, Parreira VF, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of hypocapnic hyperventilation on the response to hypoxia in normal subjects receiving intermittent positive-pressure ventilation. Chest. 2002; 121:1141-8.

4. Moosavi SH, Golestanian E, Binks AP, Lansing RW, Brown R, Banzett RB. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. J Appl Physiol 2003; 94:141-154.

5. Campbell EJM. The role of the scalene and sternomastoid muscles in breathing in normal subjects; an electromyographic study. J Anat. 1955; 89:378-86.

6. Tobin MJ, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. Ann Intensive Care. 2020 Jun 9; 10(1):78.

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202007-2940LE

On Happy Hypoxia and on Sadly Ignored "Acute Vascular Distress Syndrome" in COVID-19 Patients

Vincent Jounieaux, MD, PhD[1], Daniel Oscar Rodenstein, MD, PhD[2], Yazine Mahjoub, MD, PhD[3]

[1] Respiratory Department. University Hospital Centre. Amiens. France

[2] Emeritus Professor Cliniques universitaires Saint-Luc, Université Catholique de Louvain. Brussels. Belgium

[3] Cardiac, Thoracic-vascular and Respiratory Intensive Care Unit. Department of anesthesia and Critical Care. University Hospital Centre. Amiens. France

Correspondance to :

Professeur Vincent Jounieaux

Head of the Pneumology Department.

University Hospital Centre. Amiens. France

Corresponding author

Email: jounieaux.vincent@chu-amiens.fr

Phone: + 33 3 22 45 59 05

(595 words)

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202006-2521LE

To the Editor,

We read with great interest the article by Tobin et al. [1] on the issue of silent hypoxemia also known as happy hypoxia, a nice review of physiologic mechanisms of dyspnoea. The authors refer to the definitions and mechanisms of dyspnoea in relation to blood gases, pulmonary insults, age and disease. They also discuss the definitions and effects of hypoxia, the inaccuracies of pulse saturation and the properties of the oxygen dissociation curve, as well as the mechanisms of hypoxemia in COVID-19 patients. We agree that all the physiologic concepts recalled by Tobin at al. might, in isolation or together, contribute to a blunted ventilatory response to low levels of PaO_2 and to its corollary subjective feeling of normality, or absence of dyspnoea. Among these various factors we don't believe that the poor correlation between oxygen saturation and arterial partial pressure at low levels of saturation can explain happy hypoxia, since, as shown in the vignettes of their paper, patients have not only low SpO_2 values but also very low levels of PaO_2, (that according to their figure 1 should have led to ventilation levels well above 20 l/min) yet they consistently denied any difficulty with breathing. Similarly, whereas age and diabetes have a known blunting effect on ventilatory response to hypoxia, many patients with happy hypoxia are in their 50s or 60s, where age effects are not expected to be great, and are not diabetic. Similarly, we would add that if dyspnoea is subjective, minute ventilation levels above 20 l/min require obvious use of accessory muscles and visible increases in respiratory frequency that patients with happy hypoxia do not show.

We would like to advance that the main reason for the phenomenon of happy hypoxia is the presence of hypocapnia. We have shown several years ago that hypocapnia has such a powerful braking effect on the respiratory centre that it can completely abolish any response to repeated exposure to very low SpO_2 levels in normal subjects [2]. We see no reasons why

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202006-2521LE

happy hypoxia should be limited, as Tobin et al claim, to patients without hypocapnia. By the way, hypocapnia and its consequent alkalosis would tend to shift the oxygen dissociation curve to the left, counteracting the rightwards shift due to fever.

As to the reasons for hypocapnic hypoxia without dyspnoea, there is one Tobin et al. do not mention and we believe offers the best explanation: the presence of a right-to-left intrapulmonary shunt [3]. SARS-CoV-2 is known to induce vascular proliferation in the lungs demonstrated both in anatomic and radiologic studies [4, 5]. We have demonstrated a late right-to-left intrapulmonary shunt by contrast enhanced echocardiography in one COVID-19 patient without radiologic lung lesions (unpublished observation). This right-to-left shunt will induce hypoxia, leading to a normal increase in ventilation. However, in face of a shunt, hyperventilation will not increase PaO_2 but will certainly decrease $PaCO_2$, CO_2 being more diffusible than O_2. Thus, hypocapnia would develop, abolishing any further increase in ventilation and explaining the absence of enhanced respiratory efforts and therefore of dyspnoea. This, we contend, is the initial insult of SARS-CoV-2 that has prompted us to coin the acronym AVDS for Acute Vascular Distress Syndrome [6]. When lung lesions become prominent, either ground glass opacities or consolidations, hypoxia could worsen but hypocapnia would lessen, with the consequent "normalisation" of $PaCO_2$ and appearance of feelings of difficult breathing.

In conclusion, we believe it is time now to consider the intrapulmonary shunt as the key factor in COVID-19 patients accounting for both the presence of hypoxia and the absence of dyspnoea in many of them.

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202006-2521LE

References:

1. Tobin MJ, Laghi F, Jubran A. Why COVID-19 Silent Hypoxemia is Baffling to Physicians. *Am J Respir Crit Care Med* 2020;202(3):356-360.

2. Jounieaux V, Parreira VF, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of hypocapnic hyperventilation on the response to hypoxia in normal subjects receiving intermittent positive-pressure ventilation. Chest. 2002 Apr;121(4):1141-8.

3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N Engl J Med. 2020 May 21. doi: 10.1056/NEJMoa2015432.

4. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Witkin A, Rodriguez-Lopez JM, Jo-Anne O Shepard JO, Brent P Little BP. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020 Apr 30. doi: 10.1016/S1473-3099(20)30367-4.

5. Rodenstein D, Jounieaux V, Mwenge B, Mahjoub Y.Happy Hypoxia does not defy basic biology. https://science.sciencemag.org/content/368/6490/455/tab-e-letters

6. Mahjoub Y, Rodenstein D, Jounieaux V. Severe COVID-19 disease: rather AVDS* than ARDS? (Acute Vascular Distress Syndrome). Critical Care 2020, 24:327. doi.org/10.1186/s13054-020-02972-w

AJRCCM Articles in Press. Published August 19, 2020 as 10.1164/rccm.202006-2521LE