Editorial

An Evolving Clinical Need: Discordant Oxygenation Measurements of Intubated COVID-19 Patients

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Abstract—Since the first appearance of the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) earlier this year, clinicians and researchers alike have been faced with dynamic, daily challenges of recognizing, understanding, and treating the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2. Those who are moderately to severely ill with COVID-19 are likely to develop acute hypoxic respiratory failure and require administration of supplemental oxygen. Assessing the need to initiate or titrate oxygen therapy is largely dependent on evaluating the patient’s existing blood oxygenation status, either by direct arterial blood sampling or by transcutaneous arterial oxygen saturation monitoring, also referred to as pulse oximetry. While the sampling of arterial blood for measurement of dissolved gases provides a direct measurement, it is technically challenging to obtain, is painful to the patient, and can be time and resource intensive. Pulse oximetry allows for non-invasive, real-time, continuous monitoring of the percent of hemoglobin molecules that are saturated with oxygen, and usually closely predicts the arterial oxygen content. While the sampling of arterial blood for measurement of dissolved gases provides a direct measurement, it is technically challenging to obtain, is painful to the patient, and can be time and resource intensive. Pulse oximetry allows for non-invasive, real-time, continuous monitoring of the percent of hemoglobin molecules that are saturated with oxygen, and usually closely predicts the arterial oxygen content. As such, it was particularly concerning when patients with severe COVID-19 requiring endotracheal intubation and mechanical ventilation within one of our intensive care units were observed to have significant discordance between their predicted arterial oxygen content via pulse oximetry and their actual measured oxygen content. We offer these preliminary observations along with our speculative causes as a timely, urgent clinical need. In the setting of a COVID-19 intensive care unit, entering a patient room to obtain a fresh arterial blood gas sample not only takes exponentially longer to do given the time required for donning and doffing of personal protective equipment (PPE), it involves the consumption of already sparse PPE, and it increases the risk of viral exposure to the nurse, physician, or respiratory therapist entering the room to obtain the sample. As such, technology similar to pulse oximetry which can be applied to a patient’s finger, and then continuously monitored from outside the room is essential in preventing a particularly dangerous situation of unrealized hypoxia in this critically-ill patient population. Additionally, it would appear that conventional two-wavelength pulse oximetry may not accurately predict the arterial oxygen content of blood in these patients. This discordance of oxygenation measurements poses a critical concern in the evaluation and management of the acute hypoxic respiratory failure seen in patients with COVID-19.

Keywords—SARS-CoV-2, COVID-19, Pulse oximetry, Arterial blood gas, Oxygen saturation, Hemoglobin.

ABBREVIATIONS

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
PaO₂ Partial pressure of oxygen in arterial blood
ODC Oxyhemoglobin dissociation curve
**INTRODUCTION**

Since the first appearance of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) earlier this year, clinicians and researchers alike have been faced with dynamic, daily challenges of recognizing, understanding, and treating the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2. While a somewhat inconsistent constellation of symptoms have been observed in COVID-19 patients, those who are moderately to severely ill are likely to develop acute hypoxic respiratory failure and require administration of supplemental oxygen. This oxygen therapy may be provided either non-invasively via a nasal cannula or a bilevel positive airway pressure face mask, or invasively via endotracheal intubation with mechanical ventilation.

Assessing the need to initiate or titrate oxygen therapy is largely dependent on evaluating the patient’s existing blood oxygenation status. Normally, 2% of the total oxygen carried by blood is dissolved in the plasma. This oxygen is immediately available to the body’s tissues, is measured via the partial pressure of oxygen in arterial blood (PaO2), and has a normal range of 80–100 mmHg. The remaining 98% of oxygen carried by blood is bound to hemoglobin molecules within red blood cells, thereby forming oxyhemoglobin. While the sampling of arterial blood for measurement of dissolved gases provides a direct measurement of the PaO2, it is technically challenging to obtain via an arterial puncture or requires the insertion of an arterial catheter line. These procedures are painful to the patient, and can be time-consuming and resource intensive.

In lieu of direct blood sampling, transcutaneous arterial oxygen saturation monitoring, also referred to as pulse oximetry, is often used. Pulse oximetry allows for non-invasive, real-time, continuous monitoring of the percent of hemoglobin molecules that are saturated with oxygen. This technology is based on two assumptions: (1) hemoglobin only exists in one of two states, hemoglobin or oxyhemoglobin; and (2) the only pulsations in the body tissue on which a pulse oximeter is placed are due to arterial blood flow. In essence, a pulse oximeter works by analyzing the pulsatile signal components relative to the non-pulsatile signal components of two wavelengths of light (red (660 nm) and infrared (940 nm)) as they are continuously emitted from a pair of LEDs, travel through the fingertip or earlobe on which the probe is placed, and then reach a photodetector. The photodetector generates a photoplethysmographic waveform as its output, and electrical circuits separate out the non-pulsatile and pulsatile components of these waveforms for each of the two wavelengths. The non-pulsatile components represent the absorption of the light by nonvascular tissue, venous blood, capillary blood, and arterial blood present during diastole. The pulsatile components represent absorption of the light by all four of these as well as the additional volume of arterial blood present during systole. The non-pulsatile component is used to normalize the pulsatile component of each of the two wavelengths, which theoretically removes the need for pulse oximeters to be specifically calibrated for variations in patients’ skin pigment or tissue composition. An algorithm is then used to create a ratio of the normalized red light to the normalized infrared light. Given that hemoglobin absorbs more red light than infrared light, and oxyhemoglobin absorbs more infrared light than red light, this ratio is converted into SpO2 using the Beer–Lambert Law. A normal pulse oximetry is considered to be > 95%, although what is considered “normal” may be adjusted based on patient condition or comorbidities. For example, in the case of patients with COVID-19, oxygen therapy is often titrated to maintain an SpO2 > 88%. In normal circumstances, PaO2 can then be predicted from the SpO2 using a standard oxyhemoglobin dissociation curve.

It is usually unnecessary to perform serial arterial blood gases (ABG) to directly evaluate the PaO2 of patients due to this well-proven correlation between SpO2 and PaO2. While there are several clinical conditions which may lead to a pulse oximetry reading which is not reflective of the actual tissue oxygenation status, such as in the case of carbon monoxide poisoning, or the presence of hemoglobin variants such as methemoglobin, an astute clinician is usually able to recognize these conditions and select a more appropriate oxygenation monitoring modality. As such, during the evaluation of a patient with severe COVID-19 requiring endotracheal intubation and mechanical ventilation within one of our intensive care units (ICU), it was particularly concerning to note that in the absence of a pre-existing hematologic disorder, he was observed to have an SpO2 of 100%, while his ABG revealed a PaO2 of 47 mmHg (which would normally correlate with SpO2 of approximately 87%). We herein describe multiple observations whereby the predicted PaO2 based on pulse oximetry was substantially higher than the actual PaO2 measured by ABG. We offer these preliminary observations along with our speculative causes as a timely, urgent clinical need. In the setting of a COVID-19

| Abbreviation | Description |
|--------------|-------------|
| LED          | Light emitting diode |
| SpO2         | Pulse oximetry oxygen saturation |
| ABG          | Arterial blood gas |
| ICU          | Intensive care unit |
ICU, entering a patient room to obtain a fresh ABG not only takes exponentially longer to do given the time required for donning and doffing of personal protective equipment (PPE), it involves the consumption of already sparse PPE, and it increases the risk of viral exposure to the nurse, physician, or respiratory therapist entering the room to obtain the sample. As such, technology similar to pulse oximetry which can be applied to a patients finger, and then continuously monitored from outside the room is essential in preventing a particularly dangerous situation of unrealized hypoxia in this critically-ill patient population. Moreover, an assumption of adequate oxygenation from a falsely elevated emergency department pulse oximetry reading could lead to improper triage of the patient. Hence, appreciation that pulse oximetry may be misleading in the setting of COVID-19 respiratory disease is worthy of note, and its explanation potentially informative.

METHODS

Patients with COVID-19 who required intubation with mechanical ventilation and were admitted to a COVID ICU run by surgical critical care attendings at Stony Brook University Hospital, a major academic teaching hospital, located in suburban Long Island, New York, USA were analyzed. Standard practice included obtaining routine ABGs daily at 4am, and hourly documentation of vital signs including pulse oximetry.

Due to a patient who was noted to have markedly discordant predicted PaO2 vs actual PaO2, we elected to perform a retrospective cross-sectional evaluation of patients admitted to this ICU during April 2020 who were intubated and mechanically ventilated to assess for the frequency of this discordance. This chart review initiative was part of a larger overall project which was reviewed and approved by the Stony Brook University Institutional Review Board (IRB2020-00188).

RESULTS

Of 49 patients included in this analysis (Table 1), 7 patients (14%) had a SpO2 of ≥90% with a measured PaO2 of ≤60 mmHg (Fig. 1). According to the oxyhemoglobin dissociation curve, patients with a SpO2 of at least 90% are predicted to have a PaO2 of at least 60 mmHg.15

DISCUSSION

During routine daily evaluation of patients with COVID-19 requiring intubation and mechanical ventilation, a patient with no known pre-existing hematologic disorders was observed to have an SpO2 of 100%, while his ABG revealed a PaO2 of 47 mmHg. Initially, the discordance of these oxygenation measurements were believed to be erroneous due to (1) a recorded SpO2 value without a corresponding high quality photoplethysmographic waveform, which

### TABLE 1. Arterial blood gas pH and PaO2 values compared to pulse oximetry values for patients with COVID-19 who were intubated and mechanically ventilated.

| Patient # | pH     | PaO2 (mmHg) | SpO2 (%) |
|-----------|--------|-------------|----------|
| 1a        | 7.324  | 45          | 90       |
| 2         | 7.43   | 66          | 91       |
| 3         | 7.21   | 57          | 93       |
| 4         | 7.37   | 72          | 93       |
| 5         | 7.22   | 76          | 93       |
| 6         | 7.41   | 61          | 94       |
| 7         | 7.358  | 62          | 95       |
| 8         | 7.37   | 70          | 95       |
| 9         | 7.397  | 72          | 95       |
| 10        | 7.45   | 79          | 95       |
| 11        | 7.43   | 84          | 95       |
| 12        | 7.2    | 88          | 95       |
| 13        | 7.44   | 106         | 95       |
| 14        | 7.32   | 60          | 96       |
| 15        | 7.363  | 67          | 96       |
| 16        | 7.37   | 67          | 96       |
| 17        | 7.377  | 68          | 96       |
| 18        | 7.39   | 74          | 96       |
| 19        | 7.26   | 85          | 96       |
| 20        | 7.43   | 88          | 96       |
| 21        | 7.47   | 96          | 96       |
| 22        | 7.36   | 99          | 96       |
| 23a       | 7.47   | 52          | 97       |
| 24a       | 7.43   | 55          | 97       |
| 25        | 7.273  | 62          | 97       |
| 26        | 7.37   | 79          | 97       |
| 27        | 7.42   | 81          | 97       |
| 28        | 7.262  | 82          | 97       |
| 29        | 7.451  | 82          | 97       |
| 30        | 7.44   | 108         | 97       |
| 31        | 7.38   | 131         | 97       |
| 32a       | 7.385  | 52          | 98       |
| 33        | 7.449  | 68          | 98       |
| 34        | 7.36   | 88          | 99       |
| 35        | 7.34   | 92          | 99       |
| 36        | 7.37   | 97          | 99       |
| 37        | 7.448  | 137         | 99       |
| 38a       | 7.47   | 47          | 100      |
| 39a       | 7.453  | 54          | 100      |
| 40        | 7.38   | 62          | 100      |
| 41        | 7.45   | 79          | 100      |
| 42        | 7.41   | 80          | 100      |
| 43        | 7.371  | 84          | 100      |
| 44        | 7.502  | 91          | 100      |
| 45        | 7.469  | 102         | 100      |
| 46        | 7.325  | 107         | 100      |
| 47        | 7.35   | 167         | 100      |
| 48        | 7.46   | 172         | 100      |
| 49        | 7.37   | 198         | 100      |

*Patient with a SpO2 of at least 90% and a PaO2 < 60 mmHg.
would suggest the value was an artifact from patient movement or poor tissue perfusion; (2) incorrect calibration of the machine which analyses the ABG analyzer; (3) or an issue of incorrect labeling or handling of the ABG sample specimen. However, after a cross-sectional analysis of patients in our ICU, this seemed to occur in multiple patients with COVID-19. As such, we changed our standard practice from obtaining daily ABGs to more frequently obtaining them especially when adjusting ventilator settings or in the event of a significant change a patient’s clinical status. While the cause for this discordance is not precisely known, several hypotheses are reflected.

This discordance may be related to the oxyhemoglobin dissociation curve (ODC). The expectation of a SpO2 of at least 90% corresponding to a PaO2 of at least 60 mmHg applies to normal adult hemoglobin under normal physiologic conditions. However, it is known that certain conditions can cause this curve to shift to the left, representing a greater affinity of hemoglobin for oxygen, or a shift to the right, representing a reduced affinity of hemoglobin for oxygen.15 Given that the arterial pH of many of the patients discordant for SpO2 and PaO2 was acidic, we would expect therefore the curve to shift to the right according to the Bohr effect, thereby encouraging the release of oxygen by hemoglobin.15 As such, one expects to actually see higher PaO2 than the predicted value from the normal curve. Perplexingly, this was not the case. Vogel et al. published preliminary findings which suggest that the ODC actually shifts to the left in patients with COVID-19, despite the presence of a low arterial pH, perhaps because the prolonged periods of hypoxia associated with COVID-19 may allow patients to acclimatize to the hypoxia.16 This publication, however, was contradicted by another which claims there to be no alteration in hemoglobin’s affinity for oxygen in patients with COVID-19 compared to a control, although this small sample size was not limited to mechanically ventilated patients in an ICU.3 Thus oxygen affinity may be dynamic as the disease progresses. Overall, even if there were to be some degree of a left shift of the ODC, the observed discordance between predicted and measured PaO2 still seems only partially accounted for.

A more likely explanation could be an alteration in the shape or functionality of hemoglobin or oxyhemoglobin in the setting of COVID-19. It is already known that when molecules other than oxygen bind to hemoglobin, such as carbon monoxide (carboxyhemoglobin), pulse oximetry readings can be falsely high. This is attributed to carboxyhemoglobin absorbing a comparable amount of 660 nm light as oxyhemoglobin.8 Additionally, falsely high pulse oximetry readings may be seen in patients with poorly controlled diabetes mellitus due to excess glucose in the blood stream attaching to the hemoglobin and forming glycosylated hemoglobin.8 To this end, a study which utilized computational molecular simulation suggests that SARS-CoV-2 may be able to directly attack the heme on the 1-beta chain of hemoglobin, inducing a structural alteration as well as a likely alteration in oxygen-carrying functionality.5 Furthermore, SARS-CoV-2 induced structural alterations may be complicated by chloroquine mediated structural changes in glycosylated hemoglobin, as at the time, most of our
patients hospitalized with COVID-19 received hydroxychloroquine for an average of 5–10 days as a treatment arm.\textsuperscript{12} Finally, this acquired, variant hemoglobin may result in misleading SpO\textsubscript{2} readings, as is the case for fetal hemoglobin, which becomes saturated with oxygen at a lower PaO\textsubscript{2} than adult hemoglobin.\textsuperscript{8}

This altered hemoglobin, in its oxygenated or deoxygenated state, may be erroneously measured by the existing conventional two-wavelength pulse oximetry. As more data evolves regarding the structure and function of hemoglobin in the setting of COVID-19, we propose drawing from existing solutions for mitigating misleading pulse oximetry readings. A first step could be determining the wavelengths of light which are best absorbed by this altered hemoglobin in its oxygenated and deoxygenated states. This could then be analyzed relative to the absorption of light by normal hemoglobin and oxyhemoglobin. This technology is already seen seen in multi-wavelength co-oximeters which are able to distinguish between oxyhemoglobin, deoxyhemoglobin, carboxyhemoglobin, and methemoglobin.\textsuperscript{8} While the gold standard for evaluation of carboxyhemoglobin is \textit{via} direct sampling of the blood, transcutaneous multi-wave pulse oximetry has been shown to be a reasonably precise non-invasive alternative for screening patients suspected of having carbon monoxide poisoning.\textsuperscript{13} As such, perhaps the yet-to-be determined wavelengths for this suspected SARS-CoV-2 hemoglobinopathy could be added to a next-generation of multi-wavelength pulse co-oximeters.

\textbf{Conclusions}

Our preliminary observations suggest a dynamic evolution of a clinical need for accurate transcutaneous, real-time monitoring the oxygenation status of patients requiring intubation and mechanical ventilation due to COVID-19, which can be continuously monitored from a remote location. It would appear that conventional two-wavelength pulse oximetry may not accurately predict the arterial oxygen content of blood in these patients. This discordance of oxygenation measurements poses a critical concern in the evaluation and management of the acute hypoxic respiratory failure seen in patients with COVID-19.

\textbf{CONFLICT OF INTEREST}

The authors have no financial conflicts of interest to disclose.

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