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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 hypoxemic 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. 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 sparce 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. 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 hypoxemic 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 corona virus 2
PaO_2	Partial pressure of oxygen in arterial blood
ODC	Oxyhemoglobin dissociation curve

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LED	Light emitting diode
SpO2	Pulse oximetry oxygen saturation
ABG	Arterial blood gas
ICU	Intensive care unit

INTRODUCTION

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.[7] 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 hypoxemic respiratory failure and require administration of supplemental oxygen.[2,9,14] 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.[4] This oxygen is immediately available to the body's tissues, is measured *via* the partial pressure of oxygen in arterial blood (PaO_2), 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.[4] While the sampling of arterial blood for measurement of dissolved gases provides a direct measurement of the PaO_2, 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 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.[4,10,11,17,18] 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.[4,6,17] 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.[4,17] The non-pulsatile components represent the absorption of the light by nonvascular tissue, venous blood, capillary blood, and arterial blood present during diastole.[4,17] 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.[4,17] 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.[4] 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 SpO_2 using the Beer–Lambert Law.[1,8] 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 $SpO_2 > 88\%$. In normal circumstances, PaO_2 can then be predicted from the SpO_2 using a standard oxyhemoglobin dissociation curve.[6,15]

It is usually unnecessary to frequently perform serial arterial blood gases (ABG) to directly evaluate the PaO_2 of patients due to this well-proven correlation between SpO_2 and PaO_2. 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 SpO_2 of 100%, while his ABG revealed a PaO_2 of 47 mmHg (which would normally correlate with SpO_2 of approximately 87%). We herein describe multiple observations whereby the predicted PaO_2 based on pulse oximetry was substantially higher than the actual PaO_2 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

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 sparce 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 PaO_2 vs actual PaO_2, 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 SpO_2 of $\geq 90\%$ with a measured PaO_2 of ≤ 60 mmHg (Fig. 1). According to the oxyhemoglobin dissociation curve, patients with a SpO_2 of at least 90% are predicted to have a PaO_2 of at least 60 mmHg.[15]

TABLE 1. Arterial blood gas pH and PaO_2 values compared to pulse oximetry values for patients with COVID-19 who were intubated and mechanically ventilated.

Patient #	pH	PaO_2 (mmHg)	SpO_2 (%)
1[a]	7.324	45	90
2	7.43	66	91
3[a]	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
23[a]	7.47	52	97
24[a]	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
32[a]	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
38[a]	7.47	47	100
39[a]	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

[a]A patient with a SpO_2 of at least 90% and a $PaO_2 < 60$ mmHg.

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 SpO_2 of 100%, while his ABG revealed a PaO_2 of 47 mmHg. Initially, the discordance of these oxygenation measurements were believed to be erroneous due to (1) a recorded SpO_2 value without a corresponding high quality photoplethysmographic waveform, which

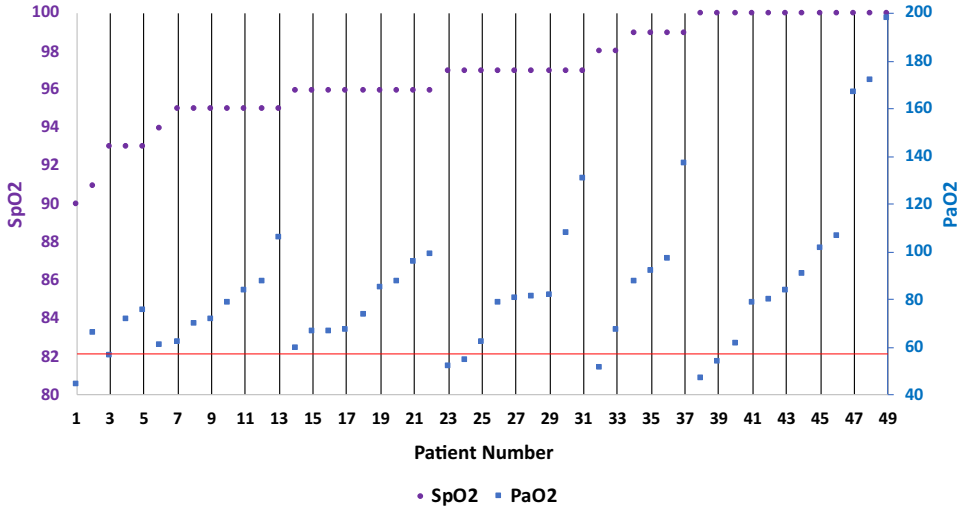

FIGURE 1. Scatter diagram depicting the SpO_2 (left *Y* axis) and PaO_2 (right *Y* axis) of each of the 49 patients (*X* axis). The horizonal red line indicates a PaO_2 of 59 mmHg.

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 SpO_2 of at least 90% corresponding to a PaO_2 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 SpO_2 and PaO_2 was acidemic, 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 PaO_2 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 PaO_2 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.[12] Finally, this acquired, variant hemoglobin may result in misleading SpO_2 readings, as is the case for fetal hemoglobin, which becomes saturated with oxygen at a lower PaO_2 than adult hemoglobin.[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.[8] While the gold standard for evaluation of carboxyhemoglobin is *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.[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.

Conclusions

Our preliminary observations suggests 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 hypoxemic respiratory failure seen in patients with COVID-19.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest to disclose.

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