Beyond Pulse Oximetry to Pulmonary Gas Exchange Measurement in COVID-19

Standalone Pulse Oximetry, Friend or Foe?

There is no question that stand-alone pulse oximetry has become a standard in modern healthcare. It is as ubiquitous as the stethoscope, and as heavily relied upon as the electrocardiogram. That makes it all the more concerning that suddenly, in the midst of the largest respiratory crisis the world has ever faced, healthcare providers are wondering if this long-held lynchpin of healthcare monitoring is leading them astray. Simply put, the peripheral saturation readings from stand-alone pulse oximetry (i.e., SpO_2% values) are not correlating with the clinical realities of the patients in front of them. Sometimes they see patients with good saturations collapse suddenly, while others with poor saturations can hold a casual conversation with ease. Healthcare providers want answers to explain these confusing signals. This has resulted in medical staff developing complex theories about what COVID-19 might be doing to blood and its ability to carry oxygen. However, many of these theories have been dismissed. Is there something more fundamental going on here? Is there something healthcare workers have failed to recognize, even before COVID-19?

Hypoxemia is Defined by PO_2 (P_aO_2) and Not by Saturation (SpO_2)

It is well-established that the majority of oxygen carried in the blood is bound to hemoglobin, a protein in red blood cells that is an efficient carrier of oxygen. In order for cells to use that oxygen at the tissue level, it must be released from the hemoglobin molecule into the plasma so it can diffuse into the cells. To understand how well oxygen is binding to hemoglobin, oxygen saturation (SO_2) is measured and to understand how much oxygen is available for cells to use, partial pressure of gas (PO_2) is measured.

Oxygen saturation (the ratio of oxygen bound to hemoglobin to total hemoglobin) is measured using a pulse oximeter that attempts to measure the blood oxygen saturation ratio non-invasively. When this saturation (S_aO_2) is measured using a pulse oximeter, it is denoted as SpO_2. A commercially available "medical grade" pulse oximeter reading should equate SpO_2 (measured) = S_aO_2 (blood based actual) with reasonable acceptability within +/-3%, as standardized by regulatory agencies such as the FDA. Notice saturation (SpO_2) is a ratio expressed in % terms, not a specific oxygen level in the blood.

The saturation ratio (referred to as "O_2 Sat") is NOT a measure of oxygen concentration. To approximate oxygen gas concentration in the lung (air) and in liquid form (circulating blood), one must measure partial pressure of gas which is directly proportional to oxygen concentration, and is expressed in mmHg (or Torr). The partial pressure of oxygen gas in the arterial blood is expressed as PaO_2. Healthy lungs should provide arterial blood with approximately 90-100 mmHg of O_2. Moderate hypoxemia is defined as a PaO_2 of less than 60 mmHg. In other words, hypoxemia is NOT based on "O_2 Sat" but based on "PO_2 values."

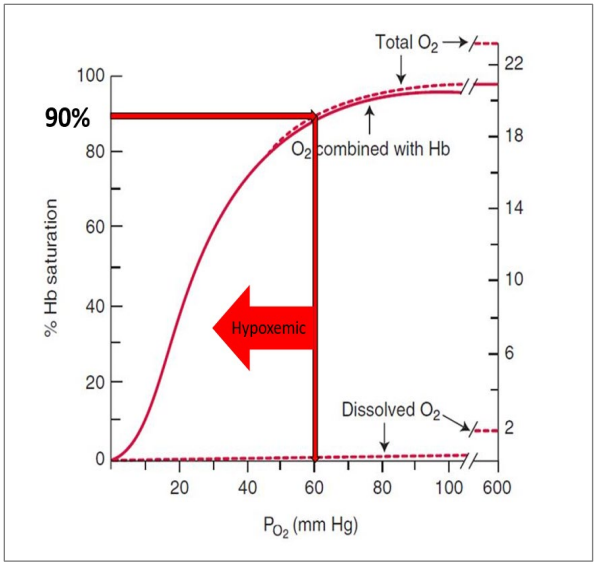

Figure 1 Oxygen-Hemoglobin Dissociation Curve Modified from John B. West's, *Respiratory Physiology: The Essentials*[1]

The Oxygen Dissociation Curve Shifts Due to Abnormal Carbon Dioxide Levels in Covid-19 Cases

The oxygen saturation (S_aO_2) and partial pressure of arterial oxygen (P_aO_2) have a sigmoidal relationship known as the Oxygen Dissociation Curve (Figure 1)[1]. An interesting feature of the curve is that it flattens as saturations rise above 90% and steeply falls off below 90%. Understanding this curve is particularly useful because one could use the saturation S_aO_2 to estimate the P_aO_2 under standard physiologic conditions. Given that obtaining a P_aO_2 measurement requires arterial blood gas sampling, which is invasive, time consuming and logistically challenging, the industry invented a non-invasive method of estimating functional oxygen saturation of arterial hemoglobin using a pulse oximeter (SpO_2) to infer oxygen level (P_aO_2) from the Oxygen Dissociation Curve.

Once an SpO_2 reading is obtained, clinicians often infer a certain P_aO_2 from the saturation reading. This convenient, non-invasive way of estimating arterial oxygenation to approximate moderate hypoxemia (<60 mmHg P_aO_2) has had countless advantages over the years. However, in a range of different pathologies, including in patients with COVID-19, the SpO_2 value alone can be critically misleading.

SpO_2 90% Rule is Insufficient

Today, many healthcare workers are wedded to a 90% SpO_2 threshold. If a patient is above 90% SpO_2, common practice is to not escalate care for that patient. If they are below 90%, the clinical staff often takes action by escalating care, such as by offering supplemental oxygen or other treatments. This rule of thumb presumes a standard Oxygen Dissociation Curve relationship with normal arterial CO_2 tension values of 40 mmHg, which is often not the case with COVID patients.

When P_aO_2 drops as a consequence of pneumonia, which commonly occurs in COVID-19, increased ventilation is stimulated. There are two primary ways patients increase ventilation: either by increasing their respiratory rate and/or by increasing the depth or volume of air with each breath.

The latter can be very challenging for clinicians to detect. Regardless of the mechanism, such elevations in ventilation can rapidly reduce CO_2. This reduction in CO_2 shifts the oxygen-hemoglobin dissociation curve to the left (Figure 2). The end result is that for a given saturation, there is a lower P_aO_2, which is the oxygen available for the body to use. This lower P_aO_2 is the result of an increased affinity of hemoglobin for oxygen, which has benefits for oxygen uptake in the lung, but can subsequently reduce oxygen unloading at the tissue level. As previously mentioned, hospital providers often set a SpO_2 threshold of 90% as significant, since they assume that at 90% saturation, the patient's P_aO_2 is near 60 mmHg, which is the associated threshold for moderate hypoxemia. This is typically known as the "60-90 rule." However, this can be a flawed assumption where critical respiratory impairment exists. Ninety percent (90%) saturation corresponds to 60-65 mmHg for P_aO_2, only when a patient exhibits a

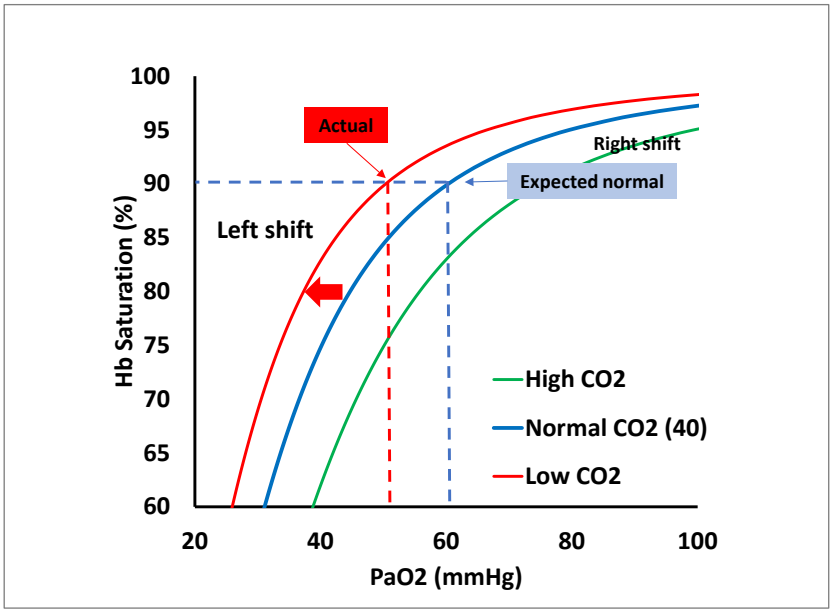

Figure 2: The impact of left and right shifts on the oxygen hemoglobin-dissociation curve due to CO_2.[1]

standard carbon dioxide level of 40 mmHg; this is often not the case in COVID patients where CO_2 values may have deviated substantially from normal values.

COVID-19 Patient Case

In a case where a patient has 91% saturation, it is assumed that the patient has a P_aO_2 in the mid-to-upper 60s. However, in an actual COVID patient case (Figure 3), the P_aO_2 is 57mmHg, not in the mid-60s as you would expect! What happened here? Failure to correct for the left-shifting effect of the oxygen dissociation curve due to a changing CO_2 level in the blood increases error in inferring P_aO_2 based on saturation. The standard assumption creates a potential blind spot regarding the patient's actual oxygenation.

Therefore, the hypoxemic patient's developing respiratory impairment (i.e., high A-a gradient) may go undetected and they may experience delayed intervention as the patient's pulse oximeter reading of 91% may not normally warrant concern. When oxygen consumption increases, due to the condition of the patient or from exertion, oxygen availability can become severely compromised. This may lead to rapid destabilization of the patient. The "sudden" deterioration of the patient can be confusing or surprising to the care team when the warning signs of respiratory compromise are missed.

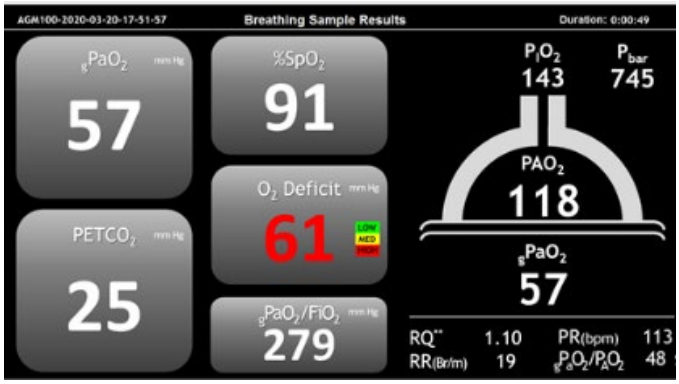

Figure 3: MediPines Respiratory Monitoring System AGM100® results screen from an actual COVID-19 patient.

The Importance of Measuring A-a Gradient (or Oxygen Deficit) for COVID-19

Dr. Martin J. Tobin, in his recent clinical study on the respiratory management of coronavirus stated,

> The dominant respiratory feature of severe coronavirus disease 2019 (COVID-19) is arterial hypoxemia…Hypoxemia accompanied by a

normal alveolar-to-arterial oxygen gradient and increase in P_aCO_2 signifies hypoventilation. Hypoventilation is uncommon with Covid-19. Instead, hypoxemia is usually accompanied by an increased alveolar-to-arterial oxygen gradient, signifying either ventilation-perfusion mismatch or intra-pulmonary shunting.[2]

Currently, A-a Gradient is obtained from the Arterial Blood Gas sampling method (ABG) which is an alternative method to the pulse oximeter, and is the most reliable procedure to determine oxygen and CO_2 levels in the blood. However, this process is invasive, logistically complicated, and time consuming, requiring an experienced clinician to perform an arterial blood extraction and then transport the sample to a centralized lab for testing. Furthermore, the alveolar oxygen value is calculated using standardized assumptions from arterial blood values from ABG. This process can take hours, which is inefficient for hospital workflow.

Is There a Better Way?

So how does one obtain the alveolar-to-arterial oxygen gradient other than using arterial blood gas measurements and performing the computation using standard assumptions in a busy hospital setting? Fortunately, there is a newly validated, non-invasive approach to obtaining a comparable measurement known as "Oxygen Deficit."

Oxygen Deficit is similar to traditional A-a gradient (from arterial blood gas sampling using a standardized equation) but done non-invasively from a breath-sampling method. Oxygen Deficit highly correlates to A-a gradient,[3] and is a measure of pulmonary gas exchange inefficiency. The higher the Oxygen Deficit (i.e., similar to high A-a gradient), the higher the degree of gas exchange inefficiency. For healthy adults at sea level, the Oxygen Deficit is typically in the single digits of mmHg. Simply put, Oxygen Deficit measures the degree of efficiency (or inefficiency) of gas exchange between the lungs and the blood. With the advent of new medical technology, the degree of respiratory impairment can now be rapidly detected with a patient's exhaled gas samples.

Practical Gas Exchange Measurements for Respiratory Impairment: MediPines AGM100®

The shape of the curve and the disproportionate impact that even a small shift can have on estimating P_aO_2 have historically made the calculation of the P_aO_2 from the saturation problematic. However, the advent of portable gas analyzers, fast and refined algorithm processors, and the technological advancement of steady state gas measurements have finally provided a highly accurate[4] and cost-effective way to detect respiratory impairment in a portable device package. The MediPines AGM100® (Figure 4) is a respiratory device designed to provide a comprehensive set of respiratory parameters and indicators via sampling from a patient's breath in a non-invasive test. It is the only commercially available, portable pulmonary gas exchange monitor that provides Oxygen Deficit, a method

Figure 4: MediPines AGM100® Respiratory Monitoring System – A Portable Respiratory Monitor

pioneered by Dr. John B. West, an eminent respiratory physiologist.

The MediPines AGM100® Respiratory Monitoring System focuses on detecting and measuring pulmonary gas exchange. It is the only US FDA cleared, Health Canada COVID-19 emergency

authorized gas exchange monitoring system currently on the market that provides accurate correction for the curve shift for non-invasive P_aO_2 calculation (Figure 4). MediPines AGM100® directly measures the lung's oxygen and carbon dioxide gas levels from taking steady state breathing gas samples, and then calculating the arterial oxygen level (P_aO_2) adjusted for the Bohr effect. It integrates these direct and calculated measurements on a single device. The respiratory monitor performs with comparable accuracy and precision within acceptable bias against the current gold standard, arterial blood gas values, in normal to hypoxic physiology scenarios.[4]

Accurate Detection Imperative

The primary function of the lung is to conduct gas exchange efficiently, but COVID-19 infection disrupts this efficiency. In hospitalized COVID-19 cases, the dominant symptoms are arterial hypoxemia combined with abnormal alveolar to arterial oxygen gradient (Oxygen Deficit), typically accompanied with low CO_2 (Figure 4).

An example of an actual hospitalized COVID patient case monitored over multiple days is provided in Figure 5. On the surface, the patient on room air seems relatively normal with a slightly low saturation (SpO_2 91-93%) that is above the desaturation threshold (~90%), which is certainly not enough to warrant intervention. Again, a pulse oximeter alone only measures oxygen saturation and misses critical CO_2 and other developing respiratory impairment. Therefore, a pulse oximeter by itself is an insufficient tool to detect impending respiratory decline (i.e., gas exchange inefficiency).

Underneath the surface "COVID pneumonia" can be readily ascertained by detecting gas exchange impairment. When dealing with gas exchange impairment (i.e., inefficiency), it is necessary to ask three fundamental questions that have a direct impact on the proper assessment, treatment choices and patient outcome:

1. **Is there a respiratory impairment?** If so, what is the degree of that impairment? The degree of impairment (i.e., gas exchange inefficiency) can be answered by referencing the Oxygen Deficit (O_2 Deficit).
2. **Is blood oxygenation sufficient** or does developing hypoxemia exist? This is best measured using blood oxygen level (gP_aO_2™).

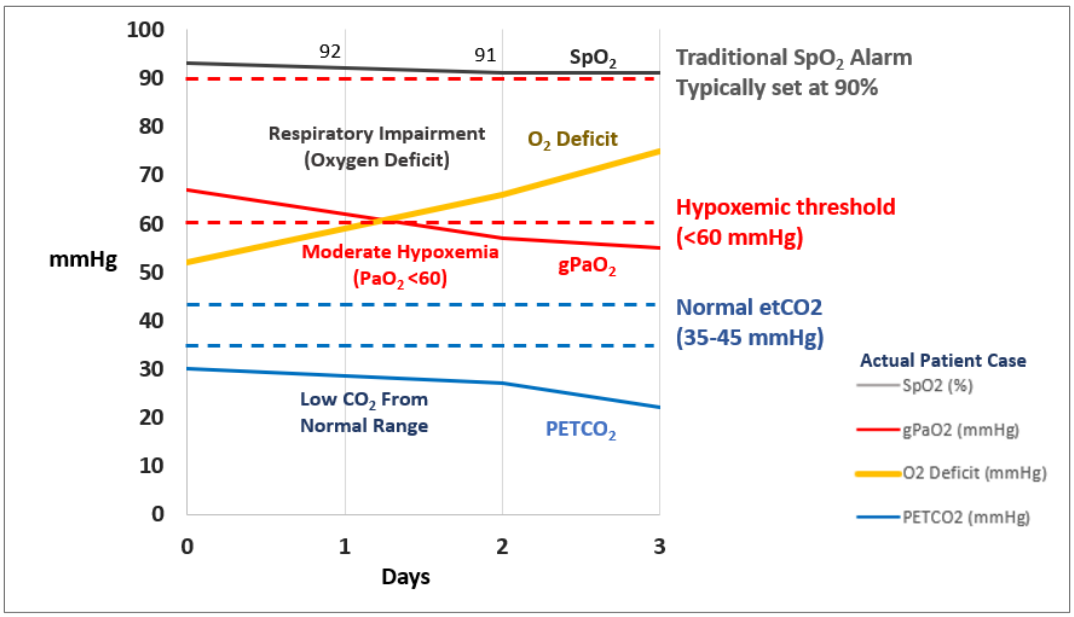

Figure 5: Actual COVID-19 patient case during hospitalization days.
Note: The unit of measure for SpO_2 is % and the units of measure for PO_2, PCO_2, O_2 deficit values are in mmHg (partial pressure); however, they are displayed on one graph for convenience.

3. **Is ventilatory effort adequate?** Is it high (i.e., hypoventilation) or is it too low (i.e., hyperventilation)? It is best to refer to carbon dioxide level ($PETCO_2$).

In the patient case shown in Figure 5, by using these three core measurements (gP_a0_2™, Oxygen Deficit, and $PETCO_2$) the medical team was able to readily recognize the need for treatment. They were able to monitor the patient's response to therapy and successfully reverse the decline, ultimately saving the patient's life. Had the medical team only relied on saturation provided by a pulse oximeter, they would have missed the declining respiratory status of the patient and would not have been able to intervene in time.

To make a difference in time-sensitive respiratory patient care, the ideal monitor should provide objective respiratory measurements that immediately answer these three fundamental questions.

Summary

In a busy clinical setting, healthcare providers strive for balance between convenience and accuracy, and are often wedded to a traditional framework such as the 60-90 rule. Although this rule is quite convenient and can be a good rule of thumb approach in normal cases, the very tools that provide some advantages can be critically misleading when dealing with the impending decline of patients with respiratory diseases such as COVID-19. The assessment of respiratory gas impairment is now imperative to support sound clinical assessment in patients presenting with COVID-19.

Definitions

SaO_2 – Oxygen saturation of hemoglobin obtained from arterial blood gas (ABG) method.

SpO_2 – Oxygen saturation of hemoglobin obtained non-invasively from a pulse oximeter. A pulse oximeter utilizes a validated light-based method that relates light absorption to empirical oxygen saturation using the co-oximetry method.

PaO_2 – Partial pressure of arterial oxygen; the oxygen level in the blood, measured in mmHg, obtained from arterial blood gas (ABG) method.

$gPaO_2$™ – Partial pressure of arterial oxygen obtained non-invasively from calculations and breathing gas sampling methods. Measured in mmHg. Exclusively provided by FDA-cleared MediPines AGM100®.

$PETCO_2$ – End-tidal carbon dioxide, commonly denoted as $etCO_2$, a measure of ventilation; the partial pressure of carbon dioxide at the end of an exhaled breath, measured in mmHg.

Oxygen Deficit (O_2 Deficit) – A-a gradient ($AaDO_2$) equivalent measured non-invasively. The difference between the alveolar (lung) and arterial (blood) levels of oxygen that represents the degree of respiratory gas exchange inefficiency, a measurement of respiratory impairment, measured in mmHg.

References

1. West, John Burnard. *Respiratory physiology: the essentials*. Lippincott Williams & Wilkins, 2012.
2. Tobin, Martin J. "Basing respiratory management of COVID-19 on physiological principles." (2020): 1319-1320.
3. West, John B., et al. "A new, noninvasive method of measuring impaired pulmonary gas exchange in lung disease: an outpatient study." Chest 154.2 (2018): 363-369.
4. Howe, Connor A., et al. "Validation of a Non-invasive Assessment of Pulmonary Gas Exchange During Exercise in Hypoxia." Chest (2020).