Advancing Respiratory Medicine®: MediPines Oxygen Deficit™

The Non-Invasive Approach to Assessing Gas Exchange Efficiency: Oxygen Deficit

Assessing the efficiency of gas exchange in patients is an important aspect of clinical management and is done by measuring the difference between the partial pressure of oxygen in the lung and arterial blood (A-aDO_2), known as the A-a gradient[11]. The value of measuring the A-a gradient is well-established, has proven clinical utility, and has been called the most informative index of the efficiency of pulmonary gas exchange[6]. The A-a gradient is obtained through blood gas analysis (ABG) with an invasive arterial puncture and has been used in pulmonary medicine for decades. However, the invasive and time-consuming nature of this test makes it less useful in acute clinical settings. Because of the logistical barriers, use of the A-a gradient has declined in favor of other less precise, but more accessible indices of oxygenation and pulmonary gas exchange[2]. The barrier to this important clinical information has finally been removed with the validation of the Oxygen Deficit, a new non-invasive approach to a traditionally unpleasant and logistically complicated procedure. The Oxygen Deficit is a surrogate measurement of the A-a gradient and represents a new approach to traditional pulmonary medicine. With only a patient's resting breath sample, the Oxygen Deficit is obtained by directly measuring alveolar oxygen and carbon dioxide gas levels, in mmHg, and calculating the arterial blood oxygen level by adjusting for the Bohr effect from oxygen saturation. The Oxygen Deficit is calculated as the difference between alveolar and arterial oxygen levels. This method results in a reproducible and reliable approach to understanding pulmonary gas exchange efficiency[11]. Now, information about gas exchange efficiency can be obtained non-invasively at the point of care.

Key Takeaways

- Oxygen Deficit is a non-invasive measure of the degree of respiratory impairment. It measures how well oxygen is being transported from the alveoli to the arterial capillary blood in the lung.
- Studies have demonstrated that Oxygen Deficit is a sensitive indicator of respiratory disease severity that is extremely useful in emergency and acute care settings.

Oxygen Deficit is sensitive to disease severity

Oxygen Deficit is a measure of gas exchange efficiency and calculated as the difference between the directly measured steady state alveolar PO_2 level in the lungs and the calculated PO_2 level in the arterial blood[7]. In the same manner as the A-a Gradient, Oxygen Deficit will help identify the cause of hypoxemia and narrow the differential diagnosis for multiple cardiopulmonary diseases. Oxygen Deficit provides important clinical information about the integrity of the alveolocapillary membrane and effectiveness of gas exchange. The most common explanations for an increased Oxygen Deficit are ventilation-perfusion mismatches, diffusion limitations, and shunting[4]. Additionally, Oxygen Deficit

is a sensitive indication of disease severity that is extremely informative in triage and acute care settings[3]. The normal range for Oxygen Deficit is 0-15 mmHg, depending on age[10]. However, in patients with gas exchange abnormalities, including COPD, heart failure, pneumonia or influenza-like diseases requiring hospitalization, Oxygen Deficit is significantly increased, with higher values indicating increasing severity of disease (Fig 1)[12]. Oxygen Deficit is only available with the pulmonary gas exchange technology contained in the MediPines AGM100™ and represents the advancement of respiratory medicine through the combination of new technology, cutting-edge hardware, and established physiological principles.

Oxygen Deficit: Healthy vs. Respiratory Patients

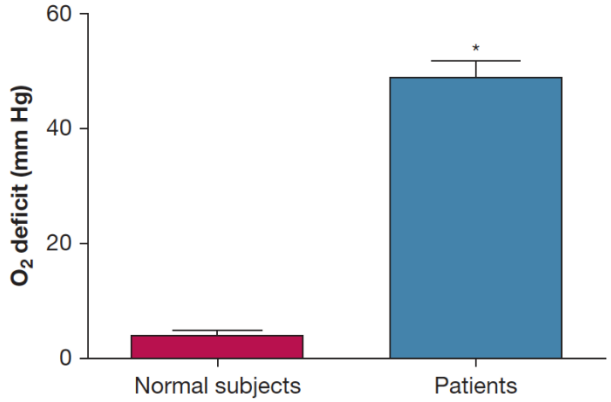

Figure 1: Reference values of Oxygen Deficit in health (n=31) and disease (n=17). Note the large difference between the two groups. P < .0001. Taken from West et al., 2018.

The Oxygen Deficit has important clinical utility as it can help narrow the differential diagnosis for hypoxemia and indicate the severity of gas exchange impairment[7]. Because the Oxygen Deficit is a surrogate measurement to the A-a gradient, we can look at decades of clinical use to incorporate this new measurement into existing clinical practice. The primary use of the A-a gradient has been in patients with hypoxemia of undetermined etiology as it will help narrow the cause of hypoxemia and allow for more direct and efficient treatment. Oxygen Deficit can be broken down categorically as either normal or elevated, and the causes of hypoxemia will fall into either category with any pathology of the alveolocapillary unit causing a higher Oxygen Deficit.

Low PaO_2 with a large Oxygen Deficit suggests oxygenation failure by poor alveolar gas exchange, caused by edema, inflammation, fibrosis, or increased pulmonary shunting. A hypoxemic patient with a normal Oxygen Deficit implies that the lungs are under-ventilating, and the patient is hypo-ventilating. Elevated Oxygen Deficit can be due to factors like V/Q mismatch in various parts of the lungs, small right to left shunts coming from the bronchial and thebesian veins, along with small pulmonary arteriovenous anastomosis, and resistance to the diffusion of oxygen across the alveolar membrane[11].

Oxygen Deficit has been used to help identify and treat a variety of cardiorespiratory complications from respiratory diseases like pneumonia, COPD, pulmonary edema, asthma, pulmonary fibrosis, lung cancer and pulmonary embolism to cardiac issues like heart failure, hypertension, and myocardial infarction[3,8,12]. Now that the Oxygen Deficit can be measured quickly at the point of care, new uses are being developed that take advantage of faster clinical information. One example of leveraging this faster clinical information is in emergency department triage and being able to discriminate between a patient that needs escalated care and a patient that can be safely sent home[3], even though both have normal oxygen saturations (Fig 4). Others are using Oxygen Deficit as a patient safety measure in a perioperative setting with pre-operative measurements setting an individualized baseline measurement for a patient and follow-up post-operative measurements able to quickly identify impending respiratory collapse well before other tools. Additionally, elevated Oxygen Deficits can assist with differential diagnosis and indicate a patient is suffering from a pulmonary embolism when it would otherwise not be suspected (Fig 3)[8].

Using the MediPines AGM100 allows healthcare providers to accurately identify hypoxemia[1] and quickly narrow the cause of hypoxemia with the information provided by alveolar PCO_2 and Oxygen Deficit. The combination of actionable clinical information can help drive efficiency in acute care settings where getting to the correct diagnosis is time-sensitive and leads to

better outcomes for patients and higher efficiency for the healthcare system.

Clinical Use Example: Oxygen Deficit in COVID-19

When a patient has a peripheral oxygen saturation of 91%, it is assumed that the patient has a PaO_2 in the mid-60s. However, in a COVID patient case (Fig 2), the PaO_2 is 57mmHg, not in the mid-60s as you would expect! This is an example of failure to correct for the left-shifting effect of the oxygen dissociation curve due to a changing CO_2 level in the blood, which increases error in inferring PaO_2 based on saturation. The standard assumption creates a potential blind spot regarding the patient's actual oxygenation.

Figure 2: MediPines AGM100 results screen from a COVID-19 patient demonstrating the left-shifting effect of the oxygen dissociation curve due to a changing CO_2 level[4].

Therefore, the developing respiratory impairment (i.e., high Oxygen Deficit) of this hypoxemic patient 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 quickly become compromised and 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.

A dominant respiratory feature of severe COVID-19 infection is arterial hypoxemia. When arterial hypoxemia is accompanied by normal Oxygen Deficit and increased $PaCO_2$, hypoventilation is indicated, which is uncommon with Covid-19. Instead, hypoxemia is usually accompanied by an increased Oxygen Deficit, signifying either ventilation-perfusion mismatch or increased intra-pulmonary shunting[4].

Clinical Use Example: Oxygen Deficit to Help Identify Pulmonary Embolism

In this case, an elderly patient came to the emergency department with shortness of breath that had persisted for weeks. The patient's history led doctors to test for myocardial infarction by ordering a cardiac panel that included ECG and blood work. Pulmonary embolism (PE) was considered as a differential diagnosis, but the risk of PE was assessed by Well's Criteria and found to be low, leading the physician to initiate treatment for a suspected heart attack. While waiting for the bloodwork results to return from the lab, the physician tested the patients pulmonary gas exchange with the AGM100 and found a severe Oxygen Deficit that could not be accounted for by a heart attack alone.

So even though the patient had no chest pain, no

Figure 3: MediPines AGM100 results screen from a Pulmonary Embolism patient indicating a severe gas exchange impairment[8].

tachycardia, no cough, a Well's score of Zero and a plausible diagnosis, the physician decided to send the patient for a chest computed tomography (CT) scan for a possible PE. The CT exam revealed a prominent thrombotic load with the lobar and segmental pulmonary arteries affecting most significantly the lower lobes. Without measuring pulmonary gas exchange with the AGM100, no one would have known the patient had an extensive pulmonary embolism! Luckily, this patient was treated appropriately,

recovered, and was discharged from the hospital days later without incident[8].

Clinical Use Example: Oxygen Deficit in Emergency Department Triage

Triaging patients with Oxygen Deficit can quickly identify those who need to be admitted to the hospital and those who can be sent home, greatly improving ER efficiency, and potentially making more beds available for patients in need. The Oxygen Deficit provides an early marker of gas exchange impairment for patients at risk of respiratory failure allowing physicians to identify them earlier, prior to obvious clinical deterioration.

Oxygen Deficit is a highly useful measure that can be used to detect severity and narrow differential diagnosis by helping to identify the source of hypoxemia and indicating the severity of gas exchange impairment. The combination of these parameters can help identify the difference between an acute heart attack and pulmonary embolism or a patient that needs immediate care compared to a patient that can be sent home[3].

A recent study indicates that an Oxygen Deficit of 40 mmHg or above is highly sensitive and specific for identifying patients who will need escalated care like supplemental oxygen. Additionally, an Oxygen Deficit of 28 mmHg or above is indicative of patients who will require hospitalization. The study demonstrated that using Oxygen Deficit as a standalone measure provided 99% accuracy indicating the important clinical decision to provide supplemental oxygen[3]. This highly accurate result demonstrates that when multiple parameters (i.e., $gPaO_2$, $PETCO_2$, and Oxygen Deficit) are used together to make clinical decisions, healthcare providers will have more confidence in the accuracy of their decisions.

Comparison of Oxygen Deficit and A-a gradient

The Oxygen Deficit is a surrogate measurement of the A-a gradient that is obtained with a new non-invasive method. The A-a gradient is obtained via Riley's "Ideal" alveolar gas method by measuring the arterial blood PO_2 through an arterial puncture and calculating the alveolar PO_2 using the Ideal Gas Equation. Alternatively, determining Oxygen Deficit utilizes the combined measurement of arterial oxygen saturation from a pulse oximeter and measurement of the end-tidal oxygen and carbon dioxide partial pressures during quiet breathing[7].

The traditional Riley method focuses on the consequences of the presence of regions of low ventilation to perfusion (V/Q) ratio that serve to add end-capillary blood with a low PO_2 to the arterial blood (venous admixture), the results being arterial hypoxemia and an increased A-a gradient. The measurement of Oxygen Deficit encompasses the effects of both low and high V/Q ratio areas, although the effect of high V/Q regions on arterial PO_2 is small because of the shape of the oxygen-hemoglobin disassociation curve. The large overlap in the areas of influence of the two methods (Fig 5) means that the

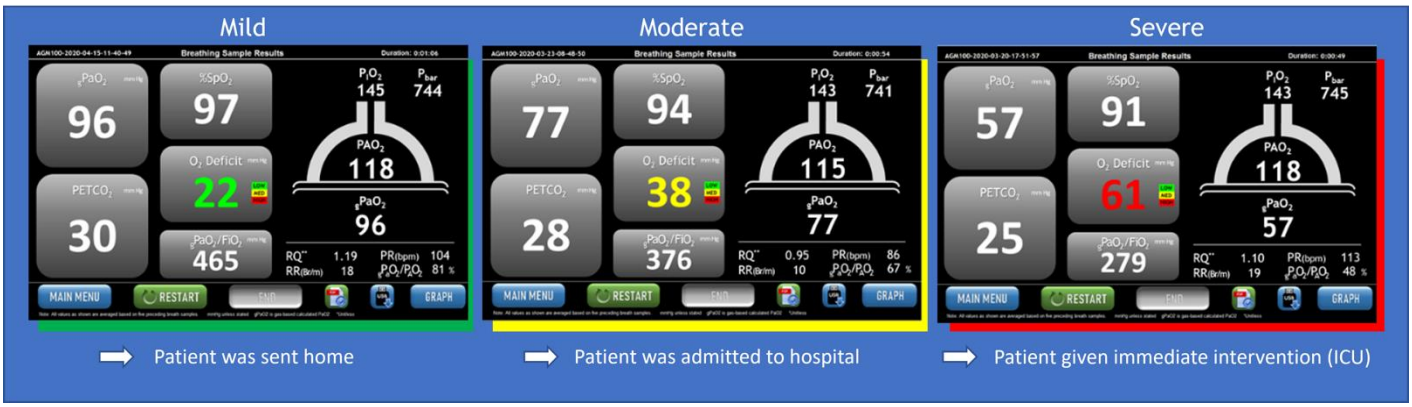

Figure 4: ***MediPines AGM100 results screen****: Emergency Department Triage example based on respiratory severity. Moderate gas exchange impairment is defined as an Oxygen Deficit between 30-60 mmHg. Severe gas exchange impairment is defined as an Oxygen Deficit ≥60 mmHg.*

two measurements would be expected to be highly correlated, albeit not the same, and this was demonstrated with a strong correlation between measures of A-a gradient and Oxygen Deficit by West and colleagues in multiple publications[1,11,12].

The MediPines AGM100 gas exchange monitor provides the difference between the end-tidal PO_2 and the calculated arterial PO_2. Fig 5 shows a graphic display of this value, and how it compares with the traditional A-a gradient using the calculated PO_2 of ideal alveolar gas. This classical oxygen – carbon dioxide diagram shows the gas composition of lung units for all ventilation-perfusion ratios from zero, the value for mixed venous blood, to infinity, the value of inspired gas[5]. For simplification, the diagram shows the inspired PO_2 and PCO_2 to be those of air at sea level, and the mixed venous point is that for the normal lung with a PO_2 of 40 and PCO_2 of 45 mmHg. The V/Q line shows all possible values for the PO_2 and PCO_2 throughout the lung.

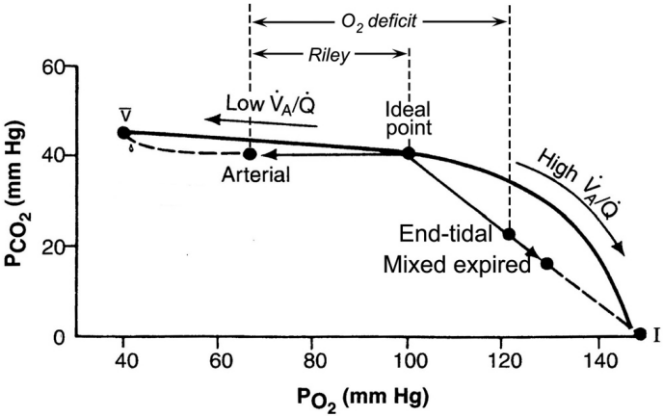

Figure 5: Classic oxygen-CO2 diagram by Rahn and Fenn with the V/Q line joining the points for mixed venous blood and inspired gas as described by JB West et. al., [5,12]

The ideal point in Figure 5 shows the location of the alveolar and arterial points for a lung with no V/Q inequality. However, in the presence of lung disease and the accompanying V/Q inequality, the arterial and alveolar points diverge from the ideal point along their respective R lines. The resulting positions of the arterial and alveolar points will depend on the pattern of V/Q inequality. For example, lung disease that results in a large fraction of the pulmonary blood flow going to lung units with abnormally low V/Q ratios will cause the arterial point to move farther to the left along the blood R line. By contrast, disease that increases the ventilation to lung unit with abnormally high V/Q ratios will cause the alveolar point to move farther down the gas R line. However, irrespective of the pattern of V/Q inequality, the O_2-CO_2 diagram with the classical Riley analysis will still result in an ideal point on the V/Q ratio line, with the arterial and alveolar points radiating from it on the respective R lines as shown in Fig. 5[12].

The movement of the arterial point away from the ideal point will cause an increase in the ideal alveolar-arterial oxygen difference, which will be displayed in the Riley analysis. However, the movement of the alveolar point will not be included in this analysis because the difference between the ideal and arterial points will not be affected. Thus, only the movement of the arterial point along the blood R line away from the ideal point will cause an increase in the Riley A-aDO_2 difference. By contrast, the movement of the alveolar point will increase the Oxygen Deficit because this measures the difference between the alveolar and arterial points[11].

It is reasonable to question what additional information is gained by measuring the Oxygen Deficit as opposed to simply measuring peripheral oxygen saturation with SpO_2. While both V/Q mismatch and shunt will serve to decrease arterial PO_2 (and thus SpO_2) and increase Oxygen Deficit, so too will hypoventilation. Because alveolar PCO_2 is also measured, hypoventilation can readily be detected which may provide an important clinical distinction of the cause of hypoxemia in some patients. Further, the Oxygen Deficit considers the effect of changes in PCO_2 on the oxygen-hemoglobin disassociation curve. Thus, the Oxygen Deficit directly addresses the efficiency of gas exchange, in the same way that the A-a gradient does[11] and does it non-invasively with the MediPines AGM100 gas exchange monitor.

Summary

Assessing respiratory impairment precisely and accurately in patients is a critical aspect of clinical management. Traditionally, the Riley method (A-a gradient) has been the gold standard measure for gas exchange efficiency, but this approach is invasive, expensive, and time-consuming, and as a result has

limited use in acute clinical settings. However, with the development of MediPines Oxygen Deficit, gas exchange efficiency can now be measured non-invasively and quickly at the point of care. The Oxygen Deficit provides important clinical information about the integrity of the alveolar capillary membrane and the efficiency of gas exchange, which is the final goal of the human respiratory system. Elevated Oxygen Deficits indicate the severity of gas exchange impairment and assist in the differential diagnosis of cardiopulmonary diseases and treatment decisions. The MediPines Oxygen Deficit obtained from the AGM100 has proven useful in emergency, respiratory, and perioperative settings. Clinicians have used Oxygen Deficit to help identify life threatening cases such as respiratory failures, pulmonary edema, pulmonary embolism, ARDS, and severe pneumonia in patients. Its non-invasive nature and ability to provide faster clinical information make it a powerful tool for identifying respiratory severity, improving patient care, and reducing the burden of cardiorespiratory disease on the healthcare system.

Key Terms

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 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 – 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.

Ventilation/Perfusion matching – arterial oxygenation is affected by ventilation/perfusion (V/Q) matching in the lungs, which determines the degree of contact between fresh gas in the airspaces and pulmonary capillary blood. V/Q mismatch generates hypoxemia when airspaces do not receive sufficient oxygen in fresh gas to fully saturate the hemoglobin. Perfused regions that receive no ventilation at all send blood with the systemic mixed venous partial pressure of oxygen to the left heart, generating a true shunt across the lung. Admixture of blood containing unsaturated hemoglobin in the pulmonary veins and left atrium results in equilibration of oxygen among red blood cells, decreasing PaO_2 and hemoglobin saturation.

References

1. Howe, C. A., MacLeod, D. B., Wainman, L., Oliver, S. J., & Ainslie, P. N. (2020). Validation of a Noninvasive Assessment of Pulmonary Gas Exchange During Exercise in Hypoxia. *Chest*, *158*(4), 1644–1650. https://doi.org/10.1016/j.chest.2020.04.017
2. Johnson, A., Bulgarelli, L., Pollard, T., Horng, S., Celi, L. A., & Mark, R. (2023). MIMIC-IV (version 2.2). PhysioNet. https://doi.org/10.13026/6mm1-ek67.
3. McGuire, W.C., Pearce, A. K., Elliott, A.R., Fine, J., West, J.B., Prisk, G., Crouch, D. R., Malhotra, A., Use of the Alveolar Gas Meter to Predict Respiratory Deterioration in COVID-19.
4. MediPines. "Beyond Pulse Oximetry to Pulmonary Gas Exchange Measurement in COVID-19" 2020.
5. *Rahn H, Fenn WO. A Graphical Analysis of the Respiratory Gas Exchange; the O2-CO2Diagram. Washington, DC: Am Physiol Soc,1955.*
6. *Riley RL, Cournand A. Ideal alveolar air and the analysis of ventilation perfusion relationships in the lung. J Appl Physiol 49: 825–847, 1949. doi:10.1152/jappl.1949.1.12.825.*
7. Prisk, G. K., & West, J. B. (2019). Deriving the arterial PO2 and oxygen deficit from expired gas and pulse oximetry. *Journal of Applied Physiology*, *127*(4), 1067–1074. https://doi.org/10.1152/japplphysiol.01100.2018
8. *Sieck D, Ozon P, (2021). Use of a Non-Invasive Pulmonary Gas-Exchange Analyzer to Improve the Pretest Probability of Pulmonary Embolism in a Patient Classified as "Low Risk"*

9. Tobin, Martin J. "Basing respiratory management of COVID-19 on physiological principles." (2020): 1319-1320.
10. Weinberger, S. E., Cockrill, B. A., & Mandel, J. (2017). Principles of Pulmonary Medicine 7th Edition. Elsevier.
11. West, J. B., Liu, M. A., Stark, P. C., & Kim Prisk, G. (2020). Measuring the efficiency of pulmonary gas exchange using expired gas instead of arterial blood: comparing the "ideal" PO2 of Riley with end-tidal PO2. *American Journal of Physiology - Lung Cellular and Molecular Physiology*, *319*(2), L289–L293. https://doi.org/10.1152/ajplung.00150.2020
12. West, J. B., Crouch, D. R., Fine, J. M., Makadia, D., Wang, D. L., & Prisk, G. K. (2018). A New, Noninvasive Method of Measuring Impaired Pulmonary Gas Exchange in Lung Disease: An Outpatient Study. Chest, 154(2), 363–369. https://doi.org/10.1016/j.chest.2018.02.001
13. MediPines. "Short on Time and Short of Breath Respiratory Medicine's Need for Speed" 2023

The MediPines AGM100 is US FDA-cleared, Health Canada approved pulmonary gas exchange monitor that exclusively provides Oxygen Deficit, (AaDO2, aka. A-a gradient), as well as blood oxygen level (gPaO2), PETCO2, and other sensitive measurements of pulmonary gas exchange. The respiratory parameters are available from patient breathing gas sampling method typically lasting 2 minutes. Visit www.medipines.com for more information on AGM100.

MediPines.com
info@medipines.com (949) 398-4670