GE HealthCare

White paper

# Clinical Research Applications for End-Tidal Oxygen Measurement

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Clinical medical practice has used end-tidal $CO_2$ measurement for several decades for purposes that include procedural sedation, adequacy of laryngeal intubation, pediatric critical care, and cardiopulmonary resuscitation. In contrast, there have been few use cases for monitoring end-tidal oxygen. Now research has identified emerging opportunities for further clinical research on the use of end-tidal oxygen measurement as an alternative to end-tidal $CO_2$ and pulse oximetry. Researchers have found potential utility for end-tidal oxygen measurement in ventilation assessment, and in emergency department procedures including procedural sedation, assessment of ventilation/perfusion mismatch, pre-oxygenation during rapid sequence intubation, and prediction of central venous oxygen saturation.

| Legend | |
|---|---|
| $FiO_2$ | fraction inspired oxygen (%) |
| $PaO_2$ | partial pressure of oxygen in the artery |
| $etO_2$ | end-tidal oxygen |
| $PaCO_2$ | partial pressure of carbon dioxide in the artery |
| $etCO_2$ | end-tidal carbon dioxide |
| $SaO_2$ | oxygen saturation in the artery |
| $SpO_2$ | pulse oximetry |
| VE | minute ventilation (volume of air inhaled per minute) |

## Oxygen Transport

### Oxygen Utilization Basics

An exploration of the utility of respiratory gas measurement starts with an understanding of the basics of oxygenation and oxygen transport.

Oxygenation involves a series of steps that include inhalation, gas exchange, oxygen transport, oxygen delivery, oxygen extraction and exhalation. This paper provides an overview of the key steps along this path. Oxygen is central to the proper functioning of the human body, which functions optimally under aerobic conditions. The reason is that the conversion of glucose, the dominant fuel for cells, requires a high amount of oxygen to produce energy the body can utilize. This energy is more commonly referenced as adenosine triphosphate (ATP).

When oxygen is lacking (i.e. under anaerobic conditions), the metabolic processes become hampered, and alternative fuel sources are utilized to generate ATP. When tissue is exposed to anaerobic conditions for prolonged periods, tissue necrosis may ensue. For example, both stroke and myocardial infarction involve tissue necrosis as a direct result of tissue hypoxia resulting from obstructed blood flow.

The metabolic byproduct of tissue metabolism is carbon dioxide ($CO_2$), which is transported from the tissue via blood circulation and is removed during exhalation. Abnormalities affecting carbon dioxide are assessed via measurements of partial pressures within the circulation (i.e. $PCO_2$) or end-tidal measurements (i.e. $etCO_2$) collected during exhalation. Changes to lung ventilation that become clinically significant are commonly identified through these measurement modalities. For instance, under respiratory distress, where ventilation is rapid and deep, the amount of $CO_2$ cleared during exhalation increases, and this is reflected as low $PCO_2$ and low $etCO_2$. In contrast, when respiratory failure is imminent, ventilation decreases and is

reflected by increasing $PCO_2$ and $etCO_2$ values.

**Oxygen Uptake**

The air we breathe contains 21% oxygen and is commonly denoted as the fractional inspired oxygen concentration ($FiO_2$). Under medical care, the minimal $FiO_2$ that can be delivered is room air ($FiO_2$=21%). But with supplemental oxygen, the $FiO_2$ can be increased to 40% or higher with use of nasal prongs, a face mask, or forms of mechanical ventilation. In contrast, the atmospheric concentration of $CO_2$ is negligible ($FiCO_2$ = ~0%). As oxygen enters an alveolar unit during inhalation, mixed venous blood enters through capillaries that originate from the pulmonary artery. As the capillary blood traverses the alveolar unit, gas exchange occurs so that equilibration of gases occurs at the end-capillary portion of the alveolar unit.

Under normal gas exchange, the partial pressure of oxygen in the alveolus is greater than within the mixed venous circulation. For $CO_2$, the opposite exists: the mixed venous partial pressure of $CO_2$ is greater than within the alveoli. These diffusion gradients result in equilibration through the alveolar unit (Figure 1). The diffusion properties of $CO_2$ are greater than those of oxygen; as a result the equilibration between the mix-venous capillary and alveolar compartments occurs sooner during transit of blood through the alveolar unit. As much $CO_2$ is exchanged for a partial pressure difference of 5 mmHg between mixed venous and alveolar space as $O_2$ is exchanged when the partial pressure difference is 60 mmHg.[1] Therefore, within each alveolar unit, $CO_2$ equilibrates sooner than $O_2$. This is an important factor in understanding how changes in ventilation or perfusion can impact arterial or end-tidal gases.

When oxygen crosses from the alveolus into the mixed-venous capillary of the alveolar unit, that oxygen will bind to hemoglobin and be transported to the heart via the pulmonary vein. Once the oxygenated blood enters the heart, it is distributed to the tissue during each contraction of the ventricles. The oxygenated blood leaving the heart is carried predominantly bound to hemoglobin; a fraction is freely dissolved within the plasma. Abnormalities to cardiopulmonary function can impact gas exchange and result in perturbations in $PaO_2$, $PaCO_2$, $etO_2$ and $etCO_2$. Arterial hypoxemia can manifest, for example, as a result of hypoventilation.

In cases of hypoventilation, minute ventilation (VE) is reduced, impairing gas exchange at the alveolar unit. Mixed venous blood flow is not affected, while oxygen delivered into each alveolar unit is diminished; the ventilation/perfusion ratio is reduced compared to normal. What then manifests is a reduction in $PaO_2$ and $etO_2$ and an accumulation of carbon dioxide as reflected in an increased $PaCO_2$ and $etCO_2$. The oxygen gradient, which is the difference between the $FiO_2$ and $etO_2$ (e.g. $FiO_2$ - $etO_2$) is a newer concept that has been shown to correlate closely with changes in ventilation (described in more detail in a later section). The change in the oxygen gradient is the result of a static $FiO_2$ in concert with ventilatory changes that impact $etO_2$; hypoventilation will result in an increasing gradient while hyperventilation will see the gradient decrease. The partial pressure of oxygen and $etO_2$ will increase, but the hallmark finding is a decrease in $PaCO_2$ and $etCO_2$.

In the presence of a perfusion shunt (Figure 2), ventilation to the alveolar unit is unaffected, but the number of mixed-venous capillaries participating in gas exchange (i.e. alveolar units not receiving mixed-venous blood) is decreased. This results in unique changes to the gas-exchange relationship. Notably, the alveolar units affected by a perfusion shunt make no contribution to gas exchange, and the mixed-venous and end-capillary $O_2$ and $CO_2$ will be the same. Given that the lung is comprised of many alveolar units, the degree of shunt will affect $PaO_2$ levels (decrease) and $PaCO_2$ levels (increase). The magnitude of changes to $O_2$ and $CO_2$ depends on the size (or relative percentage) of alveolar units affected.

Figure 1:

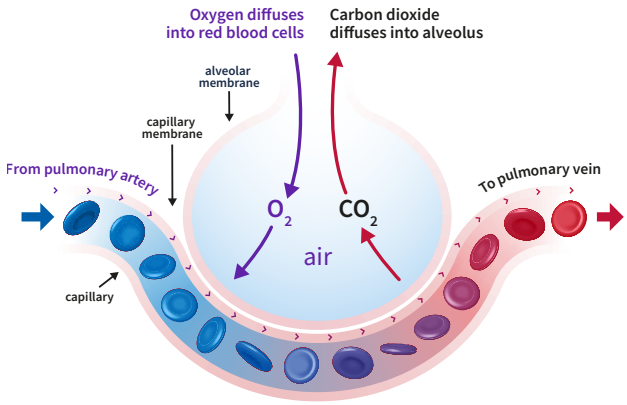
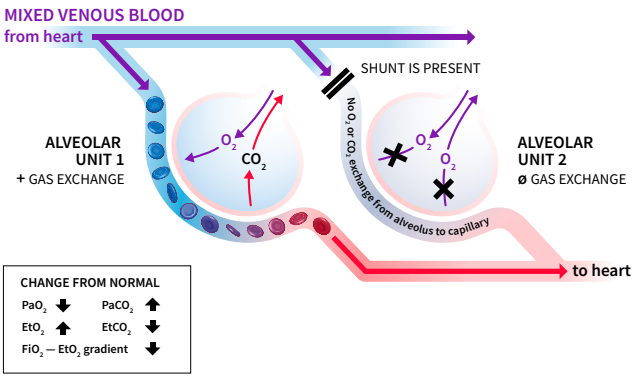
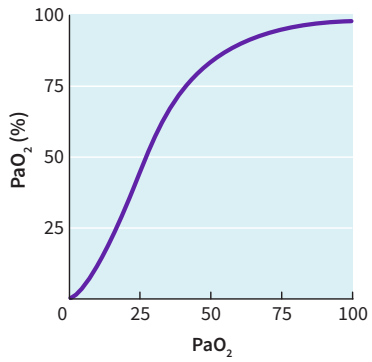



Figure 2:




The percentage of oxygen bound to hemoglobin corresponds to the degree of oxygen saturation ($SaO_2$) within the artery. The oxygen saturation dissociation curve (Graph 1) illustrates the degree of oxygen saturation for each step change in the partial pressure of oxygen ($PaO_2$). The curve is sigmoid in shape with the steepest portion in the middle of the curve. The significance of this is that minor changes in $PaO_2$ impart different changes to $SaO_2$ depending on the position along the curve. When oxygen saturation is above 92%, changes in $PaO_2$ are difficult to recognize without invasive testing such as blood gas analysis, given the flat nature of the dissociation curve.

Graph 1: Oxygen saturation dissociation curve.




Oxygen saturation is depicted as $SaO_2$ and can range from 0-100%; normal saturation is 92% or greater. Conventional patient monitors measure peripheral oxygen saturation ($SpO_2$) and are frequently used interchangeably. Mixed venous oxygen saturation follows the same oxygen dissociation principles and is depicted as $SvO_2$.

### Oxygen Delivery

The delivery of oxygen ($DO_2$) to the tissue is the product of oxygen content ($CaO_2$) of the blood and cardiac output (CO). The delivery of oxygen to the tissue is derived from the following equation(s):

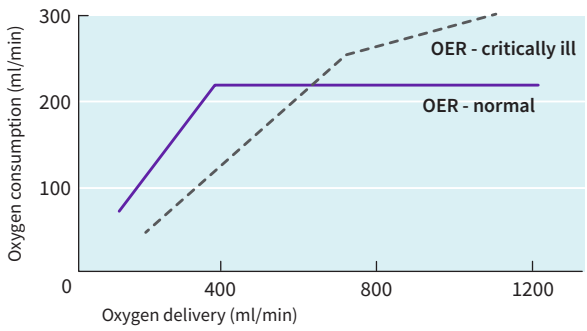
- CO = HR x SV (HR = heart rate, SV = stroke volume)
- $CaO_2 = SaO_2 \times Hb \times 1.34 + PaO_2 \times 0.003$ (Hb = hemoglobin)
- $DO_2 = CaO_2 \times CO$

Once blood is transported to the tissues, oxygen is extracted from hemoglobin in a ratio corresponding to oxygen consumption ($VO_2$); under aerobic conditions the normal extraction ratio is 25%. The oxygen extraction ratio (OER) can be represented as a relationship between oxygen delivery and oxygen consumption (Graph 2).

- $OER = VO_2/DO_2 = (SaO_2 - SvO_2)/SaO_2$

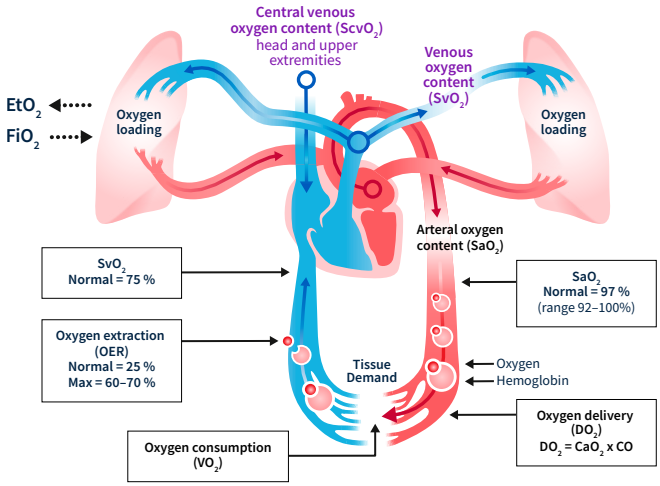
As oxygen consumption increases or oxygen delivery falls, the OER will rise in order to maintain aerobic metabolism. At the threshold where oxygen delivery can no longer fulfill oxygen consumption, anaerobic metabolism develops and there is an accumulation of oxygen debt. Oxygen debt commences when the maximum OER is attained (e.g. between 60-70%). As blood returns to the heart for re-oxygenation, the mixed venous (or central venous) oxygen saturation can be measured invasively. This measure can provide an inference to the balance between oxygen delivery and oxygen consumption.

**Graph 2:** Oxygen Extraction Ratio (OER): Relationship between oxygen delivery and oxygen consumption




To summarize, there exists a balance between oxygen intake, oxygen delivery and oxygen consumption. The figure below (Figure 3) provides a visual representation of this balance. The expiratory phase of the oxygen transport process affords the opportunity to measure end-tidal gases. Clinical practice has used end-tidal $CO_2$ for several decades. Indications for use include but are not limited to procedural sedation,[2] adequacy of laryngeal intubation,[3] pediatric critical care[4] and cardiopulmonary resuscitation.[5] In contrast, there has been a paucity of use cases for monitoring end-tidal oxygen. The subsequent sections aim to illustrate emerging opportunities for further clinical research for use of end-tidal oxygen measurements.

**Figure 3:**




Adapted from: Rivers, E. P., *et al.* (2005). "Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity." CMAJ 173(9): 1054-1065.

## Emerging Topics on End-Tidal Oxygen Measurement

Recent research has explored the utility of end-tidal oxygen measurement in a variety of clinical scenarios. Here are several applications for which end-tidal oxygen measurement has shown potential for clinical benefit.

### Ventilation Assessment

Historically, the core measures associated with monitoring respiratory function included pulse oximetry ($SpO_2$) and end-tidal $CO_2$ ($etO_2$). Both are available noninvasively and provide minute-by-minute data streams that can inform the clinician of potentially serious perturbations in respiratory status. It has been established that end-tidal $CO_2$ can serve as an estimate for $PaCO_2$ and thus inform clinicians on the ventilation and $CO_2$ elimination status of a patient.[6] However, changes in end-tidal $CO_2$ incorporate the impact of buffering of $CO_2$ within the blood and reflect a delayed view of ventilatory changes.[7,8] In the future, breath-by-breath analysis of oxygen concentration may support enhanced ventilatory status monitoring.

A study by Linko *et al.* aimed to evaluate relationships that may exist between end-tidal oxygen and arterial gas measurements during periods of hypoventilation.[8] The authors conducted a large animal study in pigs during a series of planned hypoventilation conditions. Minute ventilation was decreased by 50% and 75% from the baseline in order to measure the utility of $etO_2$ through these changes in minute ventilation. In addition, $FiO_2$ was changed through five step increments (20%, 40%, 60%, 80% and 100%).

The researchers observed an association between $etO_2$ and $PaO_2$ when the $FiO_2$ was 40% or less. As hypoventilation worsened, both $etO_2$ and $PaO_2$ decreased, and the relationship was more robust when the $FiO_2$ approximated room air. The authors introduced a gradient measure between $FiO_2$ and $etO_2$, from here on termed as the oxygen gradient. When ventilation was reduced by 50%, the $PaO_2$ fell by 23% and the $FiO_2 - etO_2$ (oxygen gradient) increased 112%, but no change in $SpO_2$ was observed. This further supports the hypothesis that $SpO_2$ as measured by pulse oximetry is an insensitive indicator of hypoventilation. The authors concluded that $FiO_2 - etO_2$ is the most sensitive parameter for detection of hypoventilation. Furthermore, increases in the $FiO_2 - etO_2$ gradient indicated an imbalance between oxygen delivery ($DO_2$) and oxygen consumption ($VO_2$), and changes in $FiO_2 - etO_2$ predicted the onset of hypoxemia earlier than $SpO_2$.

Building off of these animal results, the same authors conducted a human study during general anesthesia.[9] In this clinical study (n=20 patients), they performed breath-by-breath recording of oxygen, carbon dioxide and oxygen saturation during general anesthesia and immediately during recovery. During periods of apnea, the decreasing alveolar oxygen was detected earlier by the oxygram ($etO_2$) than by $SpO_2$. During hypoventilation, the end-tidal $O_2$ changes were identified more rapidly than changes in $etCO_2$. More important, the $FiO_2$-$etO_2$ gradient served as a more sensitive index of hypoventilation than either end-tidal $CO_2$ or pulse oximetry.

Changes in the oxygram and specifically the oxygen gradient during periods of hyperventilation have also shown promise. A study was conducted in spontaneously breathing healthy volunteers (n=10) using a T-piece system designed to attain non-rebreathing conditions.[10] Inspiratory oxygen ($FiO_2$) and carbon dioxide ($FiCO_2$) were measured along with expired oxygen ($etO_2$) and carbon dioxide ($etCO_2$) fractions and oxygen saturation ($SpO_2$). Each of the volunteers underwent a standardized sequence of ventilation (minute ventilation, VE) changes based on resting respiratory status. The first step of hyperventilation was to double VE from the baseline; five minutes thereafter the VE was tripled and held for five minutes. A simulated hypoventilation occurred thereafter - the patients were instructed to return to resting ventilation for another five minutes. This aimed to reflect a relative hypoventilation condition. There was no change to the $FiO_2$ during this sequence of ventilation interventions.

The oxygen gradient ($FiO_2$-$etO_2$) was tracked during each change in ventilation VE. The minute ventilation changed from 3.3 liters m-2 min-1 at rest, to 6.4 at 5 minutes ($p<0.01$), 8.4 at 10 minutes ($p<0.01$) and 2.5 ($p<0.01$) at 15 minutes. This latter measure reflected the relative hypoventilation state when compared to the 10-minute mark of 3x VE.

In summary, there is limited evidence to suggest that end-tidal oxygen measurement has clinical utility in the assessment of hypoventilation that trumps the use of pulse oximetry. The utility of $etO_2$ monitoring is optimal when the $FiO_2$ is between 21-40%. The use of supplemental oxygen beyond 40% does not provide clinically meaningful information because the sensitivity of the $FiO_2 - etO_2$ relationship degrades. In the study, the oxygen gradient ($FiO_2$-$etO_2$) changed from a baseline value of 48 mm Hg to 29 mm Hg at 5 min and 22 mm Hg at 10 min (all $p<0.01$)*. During the period of relative hypoventilation, the oxygen gradient increased to 62 mm Hg ($p<0.05$). End-tidal $CO_2$ changes during the experiment showed a resting value of 45 mm Hg, decreasing to 34 mm Hg at 5 minutes, 27 mm Hg at 10 minutes, and increasing to 40 mm Hg at 15 minutes (all $p<0.01$). Pulse oximetry showed modest changes of 96.3%, 97.2%, 97.6% and 92.9% at rest and at 5, 10 and 15 minutes, respectively.

In this study, the oxygen gradient ($FiO_2$-$etO_2$) showed an inverse relationship to VE, and for a 50% decrease in VE the oxygen gradient increased by 50%. The changes in oxygen gradient were more rapid than changes in end-tidal $CO_2$. In addition, the relative change in oxygen gradient was larger than that of $etCO_2$. In contrast, oxygen saturation showed modest changes during the sequence of hyperventilation steps. Therefore, the authors concluded that the oxygen gradient ($FiO_2$-$etO_2$) could provide earlier indications of changes to ventilation than conventional measurements of $etCO_2$ and $SpO_2$, especially when $FiO_2$ was ≤40%. Extrapolation to the use of the $FiO_2$-$etO_2$ gradient in spontaneous weaning trials appears to be a logical avenue for future exploration. The gradient has shown the ability to correlate with changes in minute ventilation, and it changes more quickly than changes in either $etCO_2$ or $SpO_2$. Use of the oxygen gradient may provide clinicians with an added layer of detail that can better indicate when patients are suitable for weaning.

* Data was originally presented in kPa but was converted to mm Hg using publicly available conversion calculators (https://www.checkyourmath.com/convert/pressure/kilopascals_mmhg.php)

## ED Applications of the Capnograph and Oxygraph

**Procedural Sedation**

Procedural sedation involves the use of intravenous agents used to induce a level of sedation and analgesia in order to facilitate painful procedures. In the emergency department (ED), representative procedures would include laceration repair, fracture reduction, incision and drainage, and cardioversion. Adverse events are known to occur and, while rare, some can be serious, such as apnea, bradycardia, hypotension and aspiration. Advances in procedural sedation have evolved from use exclusively within the operating theater to use more broadly within the hospital setting, including the ED.

Cardiopulmonary complications that occur during procedural sedation are often related to respiratory depression that cascades into hypoxia and cardiac decompensation. Respiratory depression can occur in up to 44% of ED cases undergoing procedural sedation.[2] Standard monitoring has included continuous pulse oximetry and cardiac monitoring throughout the procedure to provide a layer of patient safety. More recently, the use of end-tidal $CO_2$ capnography has grown in adoption to further augment patient safety. End-tidal

capnography has the benefit of recognizing respiratory depression earlier than pulse oximetry and has been found to be more sensitive than clinical evaluation. In fact, compromised respiratory function was detected 5 to 240 seconds earlier with continuous $etCO_2$ monitoring when compared to changes in pulse oximetry.[11, 12]

The premise of end-tidal capnography relies on the understanding of the ventilation and gas exchange principles that were described earlier. When intravenous agents that induce sedation or analgesia result in respiratory depression, changes in ventilation (decreased VE) will result in a decreased release of carbon dioxide during exhalation. Over time, systemic carbon dioxide will accumulate and result in an upward deflection in the $CO_2$ capnograph. When increases in $CO_2$ are observed, the clinician can be alerted to reassess the patient's airway and breathing status in order to prevent desaturation or more serious complications.

In a meta-analysis, end-tidal capnography demonstrated a significant reduction in the incidence of mild desaturation (relative risk = 0.77, 95% CI = 0.67-0.89).[13] The odds of severe desaturation ($SpO_2$ ≤85%) were also significantly reduced (RR = 0.59, 95% CI = 0.38-0.78). Assisted ventilation, which requires the use of a bag-valve mask, was shown to be favorably impacted by using $etCO_2$ monitoring; the odds ratio was significantly lower at 0.47 (95% CI = 0.23-0.95) when compared to $SpO_2$. On the whole, this meta-analysis supported the conclusion that use of end-tidal $CO_2$ capnography during procedure sedation can improve patient safety via reductions in mild desaturation, severe desaturation and assisted ventilation rates.

Building from there is the potential application of the oxygen gradient ($FiO_2$-$etO_2$), which shows a strong correlation to changes in minute ventilation as described earlier. Furthermore, the oxygen gradient has been reported to change more rapidly than $etCO_2$ and $SpO_2$ in response to hypoventilation. Could this measure add an incremental layer of patient safety to a procedure known to have the risk for respiratory complications?

**Ventilation/Perfusion Mismatch**

Efficient gas exchange at the alveoli is dependent upon matching alveolar ventilation (V) and perfusion (Q). An imbalance between these two can result from impaired ventilation or reduced perfusion and is termed a ventilation-perfusion (V/Q) mismatch. This mismatch results in suboptimal oxygenation of blood in the pulmonary artery and in turn negatively affects oxygen delivery ($DO_2$). As stated earlier, impairment in $DO_2$ can progress into anaerobic metabolism and organ damage. The hallmark condition associated with a V/Q mismatch is a pulmonary embolism, which results in a subtotal obstruction within the pulmonary arterial circulation and can be fatal depending on the degree of obstruction.

Pulmonary embolism is a medical condition that commonly presents with a combination of chest pain, shortness of breath and hypoxemia.[14] The clinical presentation can be diverse, and many diagnostic and imaging modalities have been deployed with the aim to improve the diagnostic accuracy. Diagnostic algorithms have been introduced in order to enhance the diagnostic precision of pulmonary embolism through the combination of clinical presentation, laboratory tests and diagnostic imaging modalities.[15] Paoletti *et al.* illustrated that end-tidal $CO_2$ was significantly lower while end-tidal $O_2$ was significantly higher in patients with pulmonary embolism compared to normal patients, or patients with chronic obstructive lung disease.[16] This led to the hypothesis that end-tidal $CO_2/O_2$ ratio will be lower in patients with pulmonary embolism.

Kline *et al.* conducted a study to assess the clinical utility of end-tidal $PCO_2$ and $PO_2$ as noninvasive diagnostic tools in the assessment of patients with suspected pulmonary embolism (PE).[17] Furthermore, they assessed deep exhalation or 30-second averaged end-tidal measurements obtained during normal tidal breathing. The $PO_2$, $PCO_2$ and $PCO_2/PO_2$ ratio remained stable during repeated measures across both breathing techniques. There was clear separation in $PCO_2/PO_2$ ratio between PE-positive patients compared to PE-negatives; that was observed with both deep exhalation and 30-second averaged tidal breathing measurements. Furthermore, receiver operating characteristic curves were plotted and were robust for both end-tidal breath assessments. The area under the curve (AUC) for deep exhalation was 0.728 compared to 0.803 for 30-second tidal breathing. The $PCO_2/PO_2$ cutoff that yielded a sensitivity of 95% was 0.40. Lastly, the authors combined pre-test probability with the $PCO_2/PO_2$ cutoff and concluded that this approach could provide a definite rule-in for 67.4% of patients.

This single-center study builds off of previous evidence that suggests end-tidal measurements of both oxygen and carbon dioxide can serve as an effective screening tool for suspected pulmonary embolism. This solution would be noninvasive, simple and rapid to obtain. A multi-center study conducting similar assessments would add weight to the potential clinical utility of this diagnostic approach.

**Preoxygenation During Rapid Sequence Intubation**

Another intervention central to emergency medicine practice is rapid sequence induction (RSI) and intubation to place a patient on mechanical ventilation. The first step of RSI is to preoxygenate the patient. This involves the removal of nitrogen stored within the body (denitrogenization) and replacement with oxygen. The basis for denitrogenization is to create a reservoir of oxygen within the pulmonary system that prevents hypoxia during the apneic phase of intubation. Common practice in the ED is to measure continuous $SpO_2$ during RSI; use of gas analyzers remains uncommon. Present-day gas analyzers can measure $etCO_2$ and $etO_2$ levels in real time to provide clinicians with another layer of data that informs respiratory function.

The premise of using $etO_2$ was first used in the operating theater for optimizing preoxygenation.[18, 19] Guidelines recommend that critically ill patients undergoing RSI be preoxygenated until the $etO_2$ level reaches ≥ 85%.[20] A study by Caputo *et al.* was the first conducted in the ED addressing $etO_2$ measurements in patients undergoing RSI.[21] In this two-center prospective study in patients requiring RSI, a total of 100 patients were enrolled. At the initiation of preoxygenation, the median $etO_2$ was 53%, and at the induction phase the $etO_2$ was 78%; there was no difference between use of a nonrebreather mask compared to bag-valve-mask ventilation. Only 25% (n=26) of the patients achieved a target $etO_2$ level of 85%, while 36% achieved levels between 70-85% and 27% attained levels of 50-69%. In addition, 11% did not achieve an $etO_2$ level > 50%. Desaturation below 90% occurred in 18% of patients and marked desaturation (<80%) occurred in 2% of the cases. Among the cases that experienced desaturation, only 11% had an $etO_2$ >85% at the time of induction. These authors concluded that measurement of $etO_2$ in the ED may be a valuable adjunct to optimize preoxygenation during emergency airway management requiring RSI.

Another study conducted in the ED assessed the reliability of end-tidal oxygen measurement to predict arterial oxygen ($PaO_2$) during RSI.[22] The authors specifically examined the relationship between $FiO_2$ and $etO_2$ at the time of induction to predict $PaO_2$. In this single-center prospective study, 75 patients were enrolled who required RSI for emergency airway support. Preoxygenation was controlled with a mean time of 12.5 minutes and a mean apnea time of 59 seconds. The predicted and actual $PaO_2$ were recorded within 3 minutes of intubation; the predicted $PaO_2$ was derived from an equation using $FiO_2$ and $etO_2$ values. The Pearson correlation coefficient was strong: r=0.89 (95% CI 85-92%) and the Bland-Altman plots suggested no substantial bias affecting correlation. The authors summarized that use of a gas analyzer to measure $FiO_2$ and $etO_2$ can provide a reliable measure of the minimum $PaO_2$ during RSI. Future research should explore other uses of end-tidal oximetry, this $PaO_2$ prediction equation, and other relationships to further optimize patient respiratory function.

Prediction Equation

$$PaO_2 = etO_2\ (\%) \times CC \times 760\ mmHg \times fiO_2\ (\%)$$

| | |
|---|---|
| 760 mm Hg | atmospheric pressure |
| CC | Estimated physical fitness (derived from ASA classification) |

**Prediction of Central Venous Oxygen Saturation**

Mixed venous oxygen saturation ($SvO_2$) is used commonly within the intensive care unit (ICU) and for high risk surgery (i.e. liver transplant or cardiothoracic surgery). The central venous oxygen saturation ($ScvO_2$) is commonly used in the acute care setting (ED, ICU) as a surrogate for $SvO_2$ because it is less invasive. The $SvO_2$ requires placement of a highly invasive pulmonary artery catheter within the pulmonary artery while $ScvO_2$ needs the placement of a central venous catheter within the right atrium. In both the central and mixed venous saturation, the measure is used as a surrogate for cardiac output and thus oxygen delivery ($DO_2$). Understanding oxygen delivery is critical when managing a patient with sepsis or other serious illnesses that can compromise the balance between oxygen delivery and oxygen consumption. In shock states like sepsis, the patient's $DO_2$ may be imbalanced compared to oxygen consumption ($VO_2$), and that can contribute to oxygen debt that manifests as an elevation in serum lactate. A noninvasive surrogate marker for $ScvO_2$ would be desired, especially in the ED where the majority of sepsis cases first present.

The premise behind this is the understanding of the oxygen-hemoglobin disassociation curve, where the percentage of red blood cells bound to oxygen varies with the partial pressure of oxygen in the plasma and follows a sigmoidal curve. Equilibration of the partial pressure of oxygen between the alveolus and pulmonary mixed venous capillaries (alveolar unit) occurs rapidly throughout the respiratory cycle. Therefore, one can surmise that the partial pressure of oxygen in the central blood would correlate directly with the nadir partial pressure of oxygen in a deep expired breath. This could serve as a noninvasive means to estimate $ScvO_2$.

A study conducted by Singer *et al.* aimed to assess the agreement between end-tidal oxygenation and $ScvO_2$ in critically ill patients managed in an ED setting with a central venous catheter in place.[23] This study enrolled 27 patients in a prospective observational study where $etO_2$ was measured at the time blood was drawn from a central venous line for the purpose of measuring $ScvO_2$. Modest agreement was observed via Bland-Altman plots demonstrated with bias towards $etO_2$ under-representing $ScvO_2$.

Leveraging the potential association between $etO_2$ and $ScvO_2$, a separate study was conducted by Jones *et al.*[24] in a convenience sample of patients with end-stage renal disease undergoing elective hemodialysis managed through a pre-existing central venous catheter. A side-stream analyzer was used to measure $etO_2$ and $etCO_2$ immediately after central venous blood was drawn for $ScvO_2$ analysis. Patients were instructed to perform repeated deep exhalation breathing in order to obtain an average $etO_2$ measure. In total, 21 patients were prospectively enrolled, and no significant correlation between $etO_2$ and $ScvO_2$ was identified. A linear equation incorporating $etO_2$ and $ScvO_2$ had modest predictive accuracy. Despite the lackluster findings, one limitation deserves attention. This study used a side-stream measurement technology that could have resulted in inaccurate measurements and deep expiratory breathing may not be representative of the $ScvO_2$. In addition, a methodological design that considers the use of tidal breathing over 30 seconds to measure the average nadir $etO_2$ could be more predictive.

Clinicians for years have explored noninvasive means to evaluate patients with or at-risk of critical illness, and these include end-tidal oxygen measurements. While no strong association has been identified between $etO_2$ and $ScvO_2$ at this time, future research to examine alternate measurement techniques and waveform analysis leveraging $etO_2$ may provide additional details on clinical utility for this application.

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