Deriving the Arterial \( \text{PO}_2 \) and Oxygen Deficit from Expired Gas and Pulse Oximetry.

G. Kim Prisk and John B. West

Department of Medicine, University of California, San Diego, La Jolla CA 92093

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Address for Correspondence:
G. Kim Prisk PhD, DSc
Department of Medicine-0852
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0852
kprisk@ucsd.edu
Abstract

The efficiency of pulmonary gas exchange is often assessed by the ideal alveolar-arterial partial pressure difference (A-aDO2). Through a combination of pulse oximetry and rapidly responding gas analyzers to measure the partial pressures of O2 and CO2 in expired gas one can measure the oxygen deficit. Defined as the difference between the measured alveolar PO2 and the arterial PO2 calculated from SpO2, the oxygen deficit is a substitute for the alveolar-arterial PO2 difference. The oxygen deficit is physiologically reasonable in that it increases with age in healthy subjects and is well-correlated with the A-aDO2. To calculate arterial PO2 from saturation the saturation should be below the very flat upper part of the O2-HB dissociation curve; good estimates can be made provided the arterial O2 saturation is below ~95%. Since saturations at or above 95% imply reasonably well-maintained gas exchange efficiency, this limitation is of only minor concern. Calculations show that it is necessary to take into account the change in P50 of the O2-Hb dissociation curve based on the measured alveolar PCO2. As the measurement is designed to be non-invasive, determination of any base excess is not practical, but calculations show that the effect of assuming a zero base excess is modest, with similar small effect from an abnormal body temperature. Taken together these results show that a non-invasive assessment of pulmonary gas exchange efficiency can be obtained from subjects with below normal arterial O2 saturations through a combination of expired O2 and CO2 measurements and SpO2 made during quiet breathing.

New and Noteworthy

The details and limitations of a non-invasive measurement of pulmonary gas exchange efficiency, the oxygen deficit, are described. The oxygen deficit, calculated from expired gas measurements made during quite breathing coupled with pulse oximetry, is a good surrogate measurement of the ideal alveolar-arterial PO2 difference and does not require arterial blood gas sampling.
Introduction

Assessing gas exchange efficiency in patients is an important aspect of clinical management. This has progressed from what could be determined by physical examination and the observation of cyanosis, and has been greatly advanced by the development of blood gas electrodes and pulse oximetry. Today, it is commonplace to have the arterial oxygen saturation measured as often as systemic blood pressure during clinician encounters. This is a direct consequence of the rapid development and miniaturization of the arterial pulse oximeter which can now be obtained as a battery-powered device that can be applied to a fingertip with a result obtained in 15 seconds or less in a completely non-invasive manner.

It is well appreciated that knowledge of the arterial saturation from a pulse oximeter (SpO2) is an incomplete measure of pulmonary gas exchange status, and that if a more detailed picture is required then more comprehensive measurements are necessary. Typically, these measurements involve the collection of an arterial blood sample drawn anaerobically, and subsequently analyzed to determine the partial pressures of oxygen and carbon dioxide, the pH, and the base excess. Together these parameters provide a comprehensive picture of pulmonary gas exchange. Further, based on the arterial PO2 and PCO2, the well-established alveolar-arterial oxygen difference (A-aDO2) can readily be calculated. This uses the construct of “ideal alveolar gas” introduced by Riley (13), and the A-aDO2 is considered as a useful measure reflecting the impairment in pulmonary gas exchange that results from ventilation-perfusion inequality in the lung (16).

However, arterial blood sampling is invasive, at times uncomfortable for the patient, requires specialized skills, is time consuming, and expensive. We considered that it would be potentially useful to be able to measure a surrogate for the A-aDO2 in a non-invasive and rapid manner. Our method, which has been shown to provide a potentially useful insight into pulmonary gas exchange, 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. From this we calculate the “oxygen deficit” which can be thought of as an analogous measurement to the A-aDO2 (described in detail below). We have shown in prior publications that the oxygen deficit is very small in young healthy subjects under conditions of hypoxia, somewhat larger in older but otherwise healthy adults (19) also in hypoxia, and considerably elevated in patients with a variety of pulmonary disease (20). The oxygen deficit is well-correlated with the A-aDO2 measured using an arterial blood gas sample in patients (16).
Further, the estimated values of both arterial PO2 and PCO2 measured non-invasively correlate well with directly measured arterial blood gas values in patients (20).

Since, based on these prior studies, it appears that the non-invasive measurement of oxygen deficit is both practical and potentially useful (9), it is important that the details of the technique are well understood, that the physiological basis of the measurement is clear, and that the limitations that exist are stated. While the prior studies referred to above have outlined the measurement technique, this paper aims to provide a comprehensive description on estimating gas exchange defects using expired gas measurements, and provide clarity on the limitations of such an approach.

Methods

Estimating the oxygen deficit requires the measurement of end-tidal O2 and CO2 from expired gas measurements, and the derivation of arterial PO2 from pulse oximetry.

Measuring End-tidal O2 and CO2.

End tidal measurements of gas concentrations (or partial pressures) require rapidly responding gas analyzers in order to accurately capture the changing expired concentrations of O2 (falling) and CO2 (rising) throughout expiration. Previous studies have shown that a response time (10-90%) of ~100-150 msec is adequate to accurately determine the exhaled breath profile arising from resting breathing (2). In this case the device uses separate O2 and CO2 analyzers (available from several manufacturers), each with a response time of ~130 msec and 100 msec from 10 to 90% (respectively). Typical output from these analyzers is shown in Figure 1. These data were derived from a patient with lung disease, wearing a noseclip, breathing air quietly through a mouthpiece. The tip of the gas sampling tube was inserted through the side wall of the mouthpiece so that gas was sampled from the middle of the gas flow. The gas sampling line includes Nafion® in order to equilibrate the water vapor content of the sampled gas with ambient conditions to eliminate the dependency of the analyzer output on humidity, as recommended by the manufacturers of the gas analyzers.
End-tidal values were determined by detecting the rapid fall in CO2 and rise in O2 that occurred at the onset of inspiration as fresh inspired air was brought to the tip of the sampling tube. The data in the 0.5 seconds preceding this point were then averaged to produce the end-tidal values for O2 and CO2 for that breath incorporating approximately the last 1/5th of the expiration at a normal respiratory rate. These are plotted in the lower section of Figure 1 as a trend plot with a single value per breath plotted. This trend plot provides a visual indication of the degree of steady-state breathing being produced by the patient. The aim is to have all the end-tidal values derived from breaths that are of comparable tidal volume and which all end at FRC. To help ensure this, an indication of steady-state breathing by considering the variation in end-tidal CO2 over the last 45 seconds. This results in the steady state indicator being set as shown in the lower right corner of Figure 1. The average of the end tidal O2 and CO2 values over the last 5 breaths are shown in the top left corner of Figure 1. Partial pressures are derived based on the measured concentrations and the measured barometric pressure (PBar: upper right middle in Figure 1).
A frequent objection to using the end-tidal partial pressures as a measure of alveolar partial pressures is that their values depend on the duration of expiration. If the duration is increased, the PO$_2$ continues to fall, and the PCO$_2$ continues to rise. However, evidence shows that the end-tidal PO$_2$ is a robust measurement if a steady state has been obtained (19). In brief, the end-tidal PO$_2$ is taken as the value in the alveolar gas at the end of a relaxed expiration, or the lung volume just above this. The end expiratory lung volume is a very repeatable measurement under steady-state conditions, being determined by the elastic recoil properties of the lung and the chest wall.

Deriving the arterial PO$_2$ from the SpO$_2$.

The O$_2$-Hb dissociation curve is well known and we routinely estimate saturation from PO$_2$ measurements. In the present situation we take the inverse approach and, based on the arterial O$_2$ saturation from a pulse oximeter, we calculate the PO$_2$ in the arterial blood. Doing so requires two steps: First the P$_{50}$ of the O$_2$-Hb dissociation curve must be determined, and second, and inverse form of the relationship between PO$_2$ and saturation must be used to calculate the PO$_2$.

The O$_2$-Hb dissociation curve shifts to the left or to the right as a result of changes in PCO$_2$ (the Bohr effect), pH, temperature, and 2,3-DPG. However, by far the biggest shift is that arising from changes in PCO$_2$ as discussed in the section on the magnitude of the Bohr effect (in Results section, below). While the other effects are not unimportant they are not information that is readily available in most instances.

We used the end-tidal PCO$_2$ (measurement described above) as a measure of arterial PCO$_2$. It is well established that by virtue of the flatness of the blood-R line in the O$_2$-CO$_2$ diagram, that end-tidal PCO$_2$ and arterial PCO$_2$ values are equivalent (3), and indeed the calculation of the widely used ideal A-aDO$_2$ uses that assumption (1). We estimated the P$_{50}$ of the O$_2$-Hb dissociation curve using the Kelman routines (18). These are based on the results of published biochemical studies of the effects of changing the appropriate variables. These were applied for varying values of PCO$_2$ under the assumption that the base excess was zero, the temperature 37ºC.
Inverting the relationship between PO2 and saturation (i.e. calculating PO2 based on saturation) was based on the inversion of the Hill Equation:

\[ PO2^n = P50^n * SaO2/(1-SaO2) \]

where P50 is PO2 at a saturation of 50%. This form is readily solved digitally without inverting the equation by taking the logarithm of the equation and solving algebraically.

Oxygen deficit

The oxygen deficit was derived as the difference between the end-tidal PO2 measured as described above (that is the averaged end-tidal value over the last 5 breaths), and the calculated arterial PO2 also described above. Using the same algorithm as that incorporated in the commercial device for measuring the oxygen deficit we first examined the effects of the errors that result from incorrect assumption of a zero base excess, and from the assumption of a normal body temperature (37º C) on the calculated oxygen deficit. These represent “static” errors which would serve to make for consistent error in measurements performed on a particular subject.

Monte Carlo simulation of the oxygen deficit

The sensitivity of the calculated oxygen deficit to errors in measured SpO2 from the pulse oximeter, and to errors in the measured values of end-tidal O2 and CO2 (together these three parameters are used to calculate the oxygen deficit) was assessed by considering the effect of simultaneous assumed errors in all three using a Monte Carlo approach.

Using a fixed reference point of a PAO2 of 100 mmHg, and a PACO2 of 40 mmHg, 200 uniformly distributed values of PaO2 in the range for 40-100 mmHg were used as the input and the corresponding nominal fractional saturation values calculated using the Kelman routines. For each of these points, normally distributed random errors in fractional saturation, end-tidal PO2 and PCO2 were generated a total of 1000 times and each such set of values used as input parameters to the algorithm used to calculate PaO2 and subsequently the oxygen deficit. Random errors that resulted in fractional saturation values of >0.995 were replaced by a value
of 0.995. Thus for a given value of fractional saturation, the result was a mean value of the
oxygen deficit, and its associated standard deviation.

In order to provide realistic values of the errors in fractional saturation and in end-tidal gases
we determined the variability in individuals of these input parameters in a data set collected
with the commercial device. The data were from 37 normal subjects ranging in age from 20 to
91 totaling 597 separate measurements (approximately 16 per subject). Four values of FIO2
were used (0.21, 0.175, 0.15, 0.125). Fractional saturation showed a standard deviation of
0.008 and was slightly higher at lower values of saturation. End-tidal PO2 showed a standard
deviation of 2.7 mmHg and end-tidal PCO2 a standard deviation of 1.03 mmHg.

Based on these figures, and noting that prior studies have shown that many oximeters operate
in the range of 2% accuracy (7), we increased the standard deviation of the fractional saturation
to 0.01 units independent of the baseline value of fractional saturation. For end-tidal PO2 and
PCO2 we used standard deviation values of 3.3% and 2.7% of the value, respectively.

The Monte Carlo simulations considered simultaneous errors in O2 and CO2 in which the
deviation was assumed to be in opposite directions. This was designed to be representative of
the situation where the fluctuations in O2 and CO2 resulted from physiological changes in end-
tidal gas concentrations in which a reduction in O2 is associated with an increase in CO2 of
similar magnitude (depending on the respiratory exchange ratio).

Results

Deriving arterial PO2 from SpO2.

In order to calculate PO2 from arterial saturation, two steps are required. First, the P50 of the
O2-Hb dissociation curve must be determined, as this varies as a result of changes in PCO2 (the
Bohr effect). Second the Hill equation must be inverted using the newly derived value of P50.

Figure 2 plots a family of dissociation curves where each curve is that resulting from a different
value of PCO2, and where base excess is assumed to be zero. The values of PCO2 are indicated
for 3 curves. The intersection of each curve and the horizontal line shown at a fractional
saturation of 0.50 is the P50 for that case and these are shown for the most likely physiological
values of PCO2 (20-60 mmHg). The relationship is approximately linear with P50 increasing by
~2.2 mmHg for each 10 mmHg increase in PCO2.
Figure 2: A family of O2-Hb dissociation curves for varying values of PCO2 between 20 mmHg and 60 mmHg calculated using the Kelman routines (18). That standard dissociation curve (PCO2 40 mmHg) has a P50 of 27 mmHg and is plotted as the heavier black line. For clarity, dissociation curves for intermediate values of PCO2 are plotted only over the fractional saturation range of 0.45 to 0.55 (the short lines). The lines assume a zero value for the base excess and a temperature of 37ºC. The point where each curve crosses the horizontal line at a fractional saturation of 0.5 is the P50.

Figure 3A shows the dissociation curve that results from calculating the PO2 from saturation via the Hill equation using a Hill coefficient (the “n” in the equation) of 2.7, and a P50 of 27 mmHg. Also shown in figure 3A (crosses) are a series of measurements of reference values for PO2 and saturation published by Severinghaus (14) for “standard conditions” (pH 7.40, T 37ºC). Figure 3B shows the error in calculated PO2 compared to these reference data. Note that for values below a fractional saturation of 0.95 the error is less than 5mmHg.
Figure 3: A: The O2-Hb dissociation curve calculated from solving the Hill equation for different values of fractional saturation assuming a P50 of 27 mmHg and a Hill coefficient of 2.7 (solid line). The crosses are published reference values for the PO2 saturation relationship under standard conditions (14). B: The error in calculated PO2 from panel A compared to the reference data in panel A. Note that for the purposes of comparison with panel A, fractional saturation (the independent variable) is plotted vertically, and the error in PO2 (the dependent variable) plotted horizontally. The horizontal line at a fractional saturation of 0.94 indicates the region above which the error in calculated PO2 varies by more than 5 mmHg from the reference data and indicates the region where the calculation of PO2 from SpO2 gives results that may not be useful.

Magnitude of changes in PCO2 on calculated PO2

As Figure 2 shows, alterations in the arterial PCO2 result in a shift of the O2-Hb dissociation curve (the Bohr effect). Figure 4 shows the magnitude of the error in calculated PO2 that results from ignoring the Bohr effect. In other words, if the change in P50 resulting from a change in PCO2 shown in Figure 2 were not included, then there will be a resulting error in calculated PO2. The magnitude of this error is dependent on the SpO2 and Figure 4 shows that for values of fractional saturation that are most commonly encountered (say between 0.60 and 0.98), the effect is to underestimate PO2 if the PCO2 is low, and to overestimate the PO2 if the...
PCO2 is high. The magnitude of these errors is more than 5 mmHg in the calculated PO2 for a large (10 mmHg) change in PCO2 at higher saturation values. 

**Figure 4:** The effect of ignoring the change in P50 resulting from a value of PCO2 that is different from the nominal value of 40 mmHg on the calculated PO2. Note that the magnitude of the error increases as SpO2 increases. For fractional saturation values of 0.94 (the heavy black line in the figure) or below, the magnitude of the resulting error in PO2 remains below approximately ±5 mmHg for errors in PCO2 of up to ±10 mmHg.

Magnitude of the effect of a non-zero base excess on calculated PO2

The magnitude of a non-zero base excess was estimated by using the Kelman routines to calculate the effect of a change in base excess on the P50 of the O2-Hb dissociation curve. The results are shown in Figure 5 which shows the change in P50 from its nominal value when the
value for the base excess was raised or lowered, all other effects being held constant. It can be seen that the effect is asymmetric with a base excess of 10 mEq/l lowering the P50 by ~1.7 mmHg, and a base deficit of 10 mEq/l raising the P50 by ~4.8 mmHg. Thus, the effect of large base deficit of 10mEq/l would result in a right shift of the O2-Hb dissociation curve of 4.8 mmHg, equivalent to an error in PCO2 of ~22 mmHg (based on Figure 2). This in turn would result in an error in calculated PO2 of ~8mmHg at a fractional saturation of 0.90 (based on Figure 4). In contrast a base excess of 10 mEq/l would be the equivalent of a ~-7 mmHg change in PCO2 (Figure 2), with a resulting error in PO2 of ~-3 mmHg at a fractional saturation of 0.90 (Figure 4).
Figure 5: Change in P50 resulting from a non-zero base excess. A base excess of +10 mEq/l reduces P50 by ~2 mmHg, while a base deficit of 10 mEq/l (base excess of -10 mEq/l) causes P50 to increase by ~4.8 mmHg (indicated by the vertical lines). See text for details.

Magnitude of the effect of altered body temperature on calculated Po2

All the calculations performed above used a standard body temperature of 37ºC in the Kelman routines. However, circumstances might occur where body temperature differs from this (e.g. a fever). The P50 changes approximately linearly with temperature, increasing by ~1.7 mmHg per degree C. Thus for purposes of scale, a body temperature of (say) 39ºC would raise P50 by 3.4 mmHg, equivalent to an error in PCO2 of ~15 mmHg (based on Figure 2) which would serve to increase PO2 by ~3.5 mmHg (based on Figure 4).

Monte Carlo analysis of oxygen deficit to errors in the contributing measurements

Given the flatness of the O2-Hb dissociation curve at fractional saturation values at or above 0.95, the most likely source of variability in the oxygen deficit is error in measured saturation. These errors would be expected to increase at higher values of saturation. Figure 6 shows the results of the Monte Carlo analysis for the calculation of oxygen deficit based on errors in measured fractional saturation of 0.01 (SD), and incorporating simultaneous and opposite direction errors (the worst case scenario) of 3.3% (SD) in O2 and 2.7% (SD) in CO2.

There is a negative bias in the oxygen deficit that becomes apparent above a fractional saturation of ~0.85. Similarly, as saturation rises the variability increases as the flat upper portion of the O2-Hb dissociation curve is reached. At lower values of fractional saturation the errors in oxygen deficit remain essentially constant until a value of ~0.90 is reach, at which point the SD of the oxygen deficit begins to increase. At fractional saturation values above ~0.95, the errors in oxygen deficit become large and rapidly increase. Figure 7 shows the relationship between the calculated oxygen deficit and the AaDO2 used as input to the Monte Carlo simulation.
Figure 6: The bias and error in oxygen deficit resulting from errors in the measurement of fractional saturation coupled with simultaneous error in the measurement of end tidal O2 and CO2 in the opposite direction (a worst case scenario). A Monte Carlo simulation of 1000 points was used for each value of fractional saturation to determine the mean bias in the oxygen deficit, and its associated standard deviation (see text for details). For each of the 200 values of fractional saturation (the y-axis), the mean bias in oxygen deficit is shown in blue and that bias ± 1 standard deviation shown in red. The black symbols show the mean bias ± 1.96 SD (the 95% confidence interval). The vertical dotted line shows the case of zero bias. The horizontal dashed line at a fractional saturation of 0.95 shows that for fractional saturations above that, useful estimates of the oxygen deficit may not be practical.
Figure 7: Calculated oxygen deficit plotted as a function of the AaDO2 used as the input value to the Monte Carlo simulation. As indicated in Figure 6, at higher values of fractional saturation (and thus at low values of the AaDO2), a bias in calculated PaO2 results and this leads to the deviation from the line of identity (the dotted line).

Discussion

The major message from this paper is that obtaining a reliable estimate of the oxygen deficit based upon non-invasive measurements of expired gases and arterial oxygen saturation from a pulse oximeter is both practical and can provide valuable results. However, the shape of the
O2-Hb dissociation curve, which is nearly flat at high values of PO2, means that estimates of the oxygen deficit (which depends on the calculated arterial PO2) are both biased and highly variable at fractional saturation values of approximately 0.95 or above. Both effects are a direct result of the flat upper portion of the O2-Hb dissociation curve, with small differences in saturation resulting in large change in calculated PO2, and with the bias resulting from the fact that random errors in saturation cannot result in saturation values of greater than 100% skewing the resulting distribution of PO2 and thus oxygen deficit. Further, as shown in Figure 3B, at fractional saturation values above ~0.85, the Hill equation underestimates fractional saturation, adding to this negative bias.

At lower values of fractional saturation (below ~0.85%) the primary source of error in the calculation of oxygen deficit results not from the calculation of PaO2 from fractional saturation, but from the errors in the measurement of end-tidal O2 and CO2. This result is based on Monte Carlo simulations (not shown) in which differing levels of error in the input parameters were used allowing the individual effects of each error source to be assessed.

Comparison of the oxygen deficit with the Ideal A-aDo2

A classical means of assessing the efficiency of pulmonary gas exchange is the ideal alveolar-arterial O2 difference. In the context of this paper it is important to understand that while this is a well-accepted means of assessing pulmonary gas exchange, it relies on the artificial construct of ideal alveolar gas, a concept introduced by Riley (13). This is estimated based on the measurement of the arterial PCO2, on the assumption that this is the same as the ideal alveolar PCO2 because the blood R line on the O2 – CO2 diagram is so nearly flat, and on an assumed respiratory exchange ratio, and is long-established (3). The measured arterial PO2 is then subtracted from this calculated value to yield the A-aDO2. This is illustrated in Figure 4 of reference (16).

In contrast the oxygen deficit is based on a somewhat different construct in which the alveolar point is taken to be that measured as the end-tidal gas partial pressures. The arterial point is that calculated from the measured SpO2 with an appropriate correction for PCO2 (the Bohr effect) based on the assumption that end-tidal PCO2 is the same as arterial PCO2, something that has long been established (3). The difference between the end-tidal (alveolar) point and the calculated arterial is the oxygen deficit. Thus the oxygen deficit includes both deviations from the ideal point resulting from areas of low VA/Q, which are also included in the ideal A-
aDO2, and deviations from the ideal point resulting from areas of high \( \dot{V}_A/\dot{Q} \), which are not included in the ideal A-aDO2. However, as Figure 9 clearly shows, these constructs share a high degree of commonality and therefore one would expect a strong relationship between the oxygen deficit, and the ideal A-aDO2. Prior studies (20) show this to be the case with the \( r^2 \) of the correlation between AaDO2 and oxygen deficit in 23 patients being \(~0.73\).

In practice, the results from previous studies show that the oxygen deficit produces numbers that are physiologically reasonable. It is well established that in normal subjects without lung disease, the ideal A-aDO2 is relatively small, and that this increases with healthy ageing. When a cohort of normal subjects were tested, those categorized as “young” (19-31 yrs) had a very low oxygen deficit (averaging 2.0 mmHg), while “older” (47-88 yrs) subjects had an elevated value averaging 7.5 mmHg (19, 20). It is important to point out that these measurements were performed while the subjects were breathing a hypoxic gas mixture (FIO2 0.125) for at least 10 minutes in order to lower their otherwise normal fractional saturation values to a range where calculation of the arterial PaO2 from end-tidal measurements was practical. It is well known that for a given degree of \( \dot{V}_A/\dot{Q} \) inequality in the lung, the A-aDO2 will be lower at lower levels of inspired O2 since the arterial point will be on a steeper part of the O2-Hb dissociation curve than would be the case breathing a normoxic gas (15). Thus, the low values for the oxygen deficit in these two cohorts of normal subjects may result, at least in part, by the hypoxia imposed during measurement. While this alters the absolute values, the effect is present in both the young and older cohorts, showing a clear effect of age on the oxygen deficit, as expected.

In contrast to the data from normal subjects, a cohort of patients with a range of pulmonary diseases breathing air (FIO2 0.21) show a very much higher value for the oxygen deficit (averaging 41.9 mmHg) (20). All of these patients had fractional saturation values of 0.95 or less breathing air, and their calculated oxygen deficit was much higher than either normal cohort. In the patients studied, their underlying lung disease resulted in their oxygen saturation being <= 95% (they were selected based on this criterion) and so these measurements also occurred when they were operating on the steep potion of the O2-Hb dissociation curve. Similarly, the patient cohort had (as expected) elevated A-aDO2 values, and these are well correlated with the oxygen deficit values with an \( r^2 \) of \(~0.73\) (20).

**Appropriateness of the Error Analysis**
The Monte Carlo simulations we performed necessarily rest on the choices made in terms of the variability in the input parameters, end-tidal O2, end-tidal CO2, and fractional saturation. We based this on the observed variability in 37 subjects with ~16 measurements per subject spread across 4 values of FiO2 (a total of 597 measurements). Thus we have a high degree of confidence that the variability we used in the Monte Carlo simulations are representative to that seen in actual use. In the case of the end-tidal measurements, the observed variability in end-tidal O2 as 3.3% (SD) which, assuming a respiratory exchange ratio of 0.8, would imply a variability in end-tidal CO2 of 2.6%. The observed variability in end-tidal CO2 was 2.7%, suggesting that it was appropriate to use the opposing direction variation in O2 and CO2 in our simulations. It should also be noted that the variability in oxygen deficit that results from variability in end tidal O2 would similarly affect direct measurements of the AaDO2 for which oxygen deficit is a surrogate.

The other input measurement is the fractional saturation. Pulse oximetry is subject to confounding issues which can serve to limit accuracy, and reliability. We have no way to directly assess accuracy and if there are influences that serve to make the measurement inaccurate (e.g. poor fingertip perfusion, the presence of Met-Hb, or manufacturing issues (8)) that will necessarily result in an error in oxygen deficit. Reliability however is addressed by the Monte Carlo simulations. A large meta-analysis study showed that most models of pulse oximeter were accurate within 2% (± 1SD) with finger-tip probes (as used here) being superior to forehead probes (7). The observed variability in fractional saturation was 0.008 (SD) with slightly higher variability at lower values of fractional saturation. Based on that we used an error in fractional saturation of 0.01 (SD) as an absolute value regardless of the underlying value of fractional saturation.

**Fundamental Limitations**

The calculation of the oxygen deficit has some limitations, and these should be considered when interpreting the results.

**Validity of end-tidal gas a measure of alveolar concentration:**

It is assumed that the end-tidal gas concentrations measured in expired gas are reflective of the alveolar partial pressure of O2 and CO2. As expiration proceeds the expired value of O2 falls, and the value of CO2 rises resulting in the well-known sloping “alveolar plateau”. The slope occurs for two reasons. Firstly, continuing gas exchange means that as expiration proceeds, O2
is removed from the alveoli, and CO2 added. The magnitude of this effect depends on
metabolic rate and lung volume, but has been shown to be responsible for only a small portion
(∼10%) of the alveolar plateau slope in single breath tests (4). Secondly, the greater
contribution to the slope of the alveolar plateau and results from asynchronous emptying of
lung units with different VA/Q ratios (and thus with different values of O2 and CO2). This effect
has been utilized to provide estimates of the degree of ventilation-perfusion inequality in the
lung (17), and has been utilized in studies in situations where direct measurements of VA/Q
inequality are not possible such as diving (5) and spaceflight (10, 11). It has been shown to
provide a good correlation with measured VA/Q inequality in animal studies (12). The
implication of the majority of the observed alveolar plateau slope resulting from VA/Q
inequality is that end-tidal gas values are affected by that inequality. However, since the value
of O2 continues to fall as expiration proceeds (and CO2 continues to rise), this raises the
question of the point in expiration that the continuously changing gas concentrations should be
measured. Here we use the end-tidal value defined as the average of the gas concentration in
the half second preceding the onset of the following inspiration as the alveolar value. With the
subject breathing quietly, expiration terminates at FRC and this lung volume is highly reliable.
We provide a trend plot (lower part of Figure 1) as a visual indicator of the stability of end-tidal
values of O2 and CO2, and average the last 5 values for use in calculating the oxygen deficit.
Further by considering the variance of the end-tidal CO2 values we provide an indicator for the
operator of whether the subject is in steady-state. However, the instantaneous values of O2
and CO2 do not necessarily lie on the gas-R line (6) due to variations in expiratory flow
sequencing, cardiogenic oscillations, and other factors. Such factors were not directly included
in the Monte-Carlo simulations, although the data on variability in end-tidal values likely include
such effects. However, it remains possible that such deviations from the gas-R line have the
potential to increase the variability in the measured oxygen deficit.

**Error resulting from a non-zero base excess and temperature:**
Because the technique relies on non-invasive measurements, no correction for base excess
(should any be present) is practical. A base excess of 10 mEq/l would result in an approximately
3mmHg underestimation in PO2, raising the oxygen deficit by ∼3mmHg at a saturation of 90%.
The effect is however asymmetric and a base deficit of 10 mEq/l would lower oxygen deficit by
∼8 mmHg.

Temperature also serves to alter the PS0 of the O2-Hb dissociation curve. A 2ºC increase in
body temperature would serve to lower the oxygen deficit by ∼3.5 mmHg, all other factors
being equal.
Both base excess and temperature are the two factors that have the potential to produce biases in oxygen deficit measurement. The effect of temperature could readily be accounted for as the effect is essentially linear and independent of saturation. Accounting for base excess is more nuanced, although it might be argued that subjects with a substantial alteration in their acid-base status would be more likely to have a significant gas exchange defect, and thus have higher values of the oxygen deficit, making the effect of not accounting for base excess less of an issue.

Conclusion

A reliable and potentially valuable picture of the overall state of pulmonary gas exchange can be obtained from the combination of expired gas measurements and pulse oximetry. There are some limitations. The shape of the O2-Hb dissociation curve, which is very flat at high values of PO2, means that the accuracy estimates of the oxygen deficit falls rapidly for values of fractional saturation of approximately 0.95 or above, and there is a negative bias in the calculated oxygen deficit resulting from a combination of underestimation in PaO2 from the Hill equation, and an upper bound for the value of fractional saturation. Provided that the subject is in a steady-state in terms of breathing pattern, then the measured end-tidal values for PO2 and PCO2 are adequate to account for the Bohr effect, and to provide an end-tidal PO2 which, when combined with the estimated arterial PO2 allows the oxygen deficit to be calculated. The errors that result if the base excess is not zero, or if body temperature is not 37°C are sufficiently small that useful results can still be obtained without measuring these. The result is that a valuable picture of pulmonary gas exchange can be obtained by having the patient breathe through a tube for a few minutes and without the need for arterial blood gas sampling.

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Disclosures
The University of California San Diego has exclusively licensed technology to MediPines Corporation, Orange County, CA, to develop a device based on this work. JB West has a financial interest.

Figure Captions

Figure 1: Output from a prototype Gas Exchange Monitor. The image is a screen shot of the device when in use on a patient with lung disease breathing air. Note that the rapidly responding analyzers provide a good record of the inspired and expired waveforms of O2 and CO2. The trend plot in the lower portion of the screen allows assessment of steady-state and this is also indicated by the stability of end-tidal values and indicated lower-right.

Figure 2: A family of O2-Hb dissociation curves for varying values of PCO2 between 20 mmHg and 60 mmHg calculated using the Kelman routines (18). That standard dissociation curve (PCO2 40 mmHg) has a P50 of 27 mmHg and is plotted as the heavier black line. For clarity, dissociation curves for intermediate values of PCO2 are plotted only over the fractional saturation range of 0.45 to 0.55 (the short lines). The lines assume a zero value for the base excess and a temperature of 37ºC. The point where each curve crosses the horizontal line at a fractional saturation of 0.5 is the P50.

Figure 3: A: The O2-Hb dissociation curve calculated from solving the Hill equation for different values of fractional saturation assuming a P50 of 27 mmHg and a Hill coefficient of 2.7 (solid line). The crosses are published reference values for the PO2 saturation relationship under standard conditions (14). B: The error in calculated PO2 from panel A compared to the reference data in panel A. Note that for the purposes of comparison with panel A, fractional saturation (the independent variable) is plotted vertically, and the error in PO2 (the dependent variable) plotted horizontally. The horizontal line at a fractional saturation of 0.94 indicates the region above which the error in calculated PO2 varies by more than 5 mmHg from the reference data and indicates the region where the calculation of PO2 from SpO2 gives results that may not be useful.
Figure 4: The effect of ignoring the change in P50 resulting from a value of PCO2 that is different from the nominal value of 40 mmHg on the calculated PO2. Note that the magnitude of the error increases as SpO2 increases. For fractional saturation values of 0.94 (the heavy black line in the figure) or below, the magnitude of the resulting error in PO2 remains below approximately ± 5mmHg for errors in PCO2 of up to ±10 mmHg.

Figure 5: Change in P50 resulting from a non-zero base excess. A base excess of +10 mEq/l reduces P50 by ~2 mmHg, while a base deficit of 10 mEq/l (base excess of -10 mEq/l) causes P50 to increase by ~4.8 mmHg (indicated by the vertical lines). See text for details.

Figure 6: The bias and error in oxygen deficit resulting from errors in the measurement of fractional saturation coupled with simultaneous error in the measurement of end tidal O2 and CO2 in the opposite direction (a worst case scenario). A Monte Carlo simulation of 1000 points was used for each value of fractional saturation to determine the mean bias in the oxygen deficit, and its associated standard deviation (see text for details). For each of the 200 values of fractional saturation (the y-axis), the mean bias in oxygen deficit is shown in blue and that bias ± 1 standard deviation shown in red. The black symbols show the mean bias ± 1.96 SD (the 95% confidence interval). The vertical dotted line shows the case of zero bias. The horizontal dashed line at a fractional saturation of 0.95 shows that for fractional saturations above that, useful estimates of the oxygen deficit may not be practical.

Figure 7: Calculated oxygen deficit plotted as a function of the AaDO2 used as the input value to the Monte Carlo simulation. As indicated in Figure 6, at higher values of fractional saturation (and thus at low values of the AaDO2), a bias in calculated PaO2 results and this leads to the deviation from the line of identity (the dotted line).

References


Reference Data
Hill Equation

Fractional Saturation

$P_{O_2}$, mmHg

Downloaded from www.physiology.org/journal/jappl at UC San Diego Lib (132.239.079.038) on September 10, 2019.
O$_2$ Deficit = 1.156$^*$ A-aD$_{O2}$ − 9.148

$R^2 = 0.998$