Noninvasive measurement of pulmonary gas exchange: comparison with data from arterial blood gases

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INTRODUCTION

The origins of this new noninvasive method for determining the inefficiency of pulmonary gas exchange, with its concept of oxygen deficit as discussed here, can be traced back to the work of two groups in the United States in the 1940s. Fenn, Rahn, and Otis (5) clarified the mechanisms by which ventilation-perfusion inequality must increase the alveolar-arterial oxygen difference. These were mainly theoretical studies, and for example, the authors did not address the problem of measuring the alveolar PO2 in the presence of disease. The other group, led by Riley and colleagues (6), took advantage of their new bubble method to measure the PO2 and PCO2 in arterial blood samples. They introduced the concept of ideal alveolar gas, which was a construct based on the arterial PCO2, and this enabled them to report the ideal alveolar-arterial PO2 difference. However, neither group was able to make simultaneous measurements of alveolar gas and arterial blood, which is the basis of the oxygen deficit reported here.

In this noninvasive method, we also take advantage of the modern pulse oximeter, which can accurately measure the arterial oxygen saturation. This value is then used to calculate the arterial PO2 from the well-established oxygen dissociation curve, allowing for the Bohr effect by using the end-tidal PCO2.

METHODS

Patients. Patients were recruited from three sources: 1) those in the emergency room of the hospital, 2) those having arterial blood samples drawn to assess the results of surgical procedures (mainly pulmonary thromboendarterectomy), and 3) those who were diagnosed with emphysema and were part of an otherwise unrelated study that required arterial blood gas analysis. A total of 34 patients were recruited from those three sources. In all instances, patients were informed of the study, and measurements were made on those who volunteered to take part. The procedure was first explained to the patients, after which they signed a consent form approved by the Human Research Protection Program of the University of California, San Diego, under protocol no. 160713. Measurements were made in San Diego, at essentially sea level.

Experimental methods. The procedures for the noninvasive measurement of gas exchange using the Alveolar Gas Meter were the same as described in previous publications (9, 10). Briefly, a nose clip was applied, and the patient was asked to relax and breathe normally through a mouthpiece. A continuous sample of the inspired and
expired gases was led to a box, which contained rapidly responding PO2 and PCO2 sensors. The results of the analyses were simultaneously displayed on a screen, and examples of the tracings can be seen in the earlier publications. A fingertip pulse oximeter was worn, and the SpO2 reading was converted to an arterial PO2 using an oxygen dissociation curve, as previously described. The equation was that originally proposed by Hill, and we used an n value of 2.7 and P50 of 27 mmHg. The effects of PCO2 on the oxygen affinity of hemoglobin were taken into account by using the end-tidal PCO2 and the procedures previously described (9).

Because the Alveolar Gas Meter relies on noninvasive measurements, no correction for base excess (if any) was made. However, the magnitude of this correction is generally smaller than that for PCO2, which is accounted for. A base excess of 10 mEq/l reduces the P50 by approximately −1.6 mmHg, and a base deficit of 10 mEq/l increases P50 by ~4.8 mmHg. Not accounting for these changes results in an error in calculated arterial PO2 of approximately −0.7 mmHg for a base excess of this magnitude, and ~−1.5 mmHg for a base deficit at an arterial saturation of 60%, with smaller errors at higher saturations.

Arterial blood gases were drawn within a few minutes of the expired gas measurements. In some cases, opportunities for repeat samples from some patients occurred in six patients, two of whom had SpO2 values less than or equal to 95%. These were treated as separate subjects because the second sample occurred more than an hour after the first and because other experimental interventions (unrelated to this study) had occurred in that time interval.

Table 1 summarizes the results from all 34 studies. Note that in 11 of these the SpO2 was greater than 95%, the upper limit of our ability to calculate PO2 with a reasonable degree of certainty. Thus, there are no values for the calculated PaO2 or for the oxygen deficit in these 11 patients.

**RESULTS**

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**Oxygen deficit.** Figure 1 shows a plot of the oxygen deficit against the classical AaDO2 in the 23 patients from which arterial PO2 could be calculated. There was a wide range of AaDO2 in these patients and the oxygen deficit was strongly correlated with the AaDO2 with an r2 of ~0.72.

**Arterial PO2.** This new noninvasive method was not specifically designed to measure arterial PO2. However, this value is
part of the calculation of the oxygen deficit. Figure 2 shows the plot of the calculated arterial PO$_2$ against the value from the polarographic electrode. The calculated PaO$_2$ was well correlated with that directly measured from the arterial blood gases, with an $r^2$ of $-0.76$. Figure 3 is a Bland-Altman analysis of the data shown in Fig. 2. It can be seen that there is a bias such that, on average, values for the calculated arterial PO$_2$ are 2.7 mmHg higher than those measured from arterial blood gases. The analysis also shows that the mean and twice the SD of the values from the Alveolar Gas Meter contain all values measured from the polarographic electrode.

*Arterial PCO$_2*. Figure 4 shows the relation between the end-tidal PCO$_2$ and the PCO$_2$ as measured from an electrode. It can be seen that there is a correlation, with an $r^2$ of $-0.67$ with two outliers. Figure 5 shows a Bland-Altman analysis for PCO$_2$. There is a bias indicating that the mean of the end-tidal values is 3.6 mmHg below that of the measurements made by the blood gas electrodes. All but two of the end-tidal values fall within two standard deviations of the mean.

**DISCUSSION**

*Oxygen deficit.* The oxygen deficit is the most important product of the Alveolar Gas Meter. The oxygen deficit is a valuable index of the impairment of pulmonary gas exchange, and as such it is interesting to compare it with the ideal AaDO$_2$, which is the corresponding product of the analysis introduced by Riley et al. (6). This is shown in Fig. 2, which shows a strong correlation.

The variability can be expected if we look at the components of the two indexes. First, the oxygen deficit is made up of the end-tidal PO$_2$ and the calculated arterial PO$_2$. Both of these have sources of error. The end-tidal PO$_2$ depends heavily on there being a steady state of gas exchange. It takes some effort to persuade the patient to produce regular breaths of the same tidal volume, but experience shows that in most cases it is possible in the absence of severe respiratory distress. Next, a frequent objection to using the end-tidal PO$_2$ is that the value depends on the duration of expiration. If the duration is...
increased, the PO2 continues to fall. However, we now believe that the end-tidal PO2 is a robust measurement if a steady state has been obtained. As discussed elsewhere (9), the end-tidal PO2 is the value in the alveolar gas at functional residual capacity (FRC) or the lung volume just above this. The lung volume at FRC is a very repeatable measurement under steady-state conditions, being determined by the elastic recoil properties of the lung and the chest wall.

Turning to the ideal AaDO2, this, too, has a number of sources of variability. First, the fact that its derivation includes both the arterial PO2 and the PCO2 means that it is dependent on a steady state of variability. First, the fact that its derivation includes both the arterial PO2 and the PCO2 means that it is dependent on a steady state of variability. Second, the end-tidal PO2 is a robust measurement if a steady state has been obtained. As discussed elsewhere (9), the end-tidal PO2 is the value in the alveolar gas at functional residual capacity (FRC) or the lung volume just above this. The lung volume at FRC is a very repeatable measurement under steady-state conditions, being determined by the elastic recoil properties of the lung and the chest wall.

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The first group on the left comprises 20 Young Normal subjects aged 19–31 yr and published in Ref. 9. To ensure that their SpO2 was sufficiently low to permit calculation of the arterial PO2 and oxygen deficit, they breathed a hypoxic gas mixture with an FIO2 of 0.125, lowering their saturations into the 80% range. The mean oxygen deficit was only 2.0 mmHg, which is remarkably small. The next group, labeled Older Normals, was made up of healthy subjects with an age range from 47 to 88 yr. It is interesting that the mean oxygen deficit increased from 2.0 in the young subjects to 7.5 mmHg in the older group. This is consistent with the well-known fall in arterial PO2 with increasing age and is consistent with the reported fall in arterial PO2 from the age of 20 to 70 yr of ~6 mmHg (1). The last group in Fig. 6, labeled Patients, had a mean oxygen deficit of 42.7 mmHg.

Figure 6 emphasizes how valuable the oxygen deficit is in detecting impairment of gas exchange. The measurement is extraordinarily small in the 20 young normal subjects, and although the deficit is higher in the older normal subjects, it is still very small compared with that of the patients with lung disease.

The oxygen deficit is obtained by subtracting the calculated arterial PO2 from the end-tidal alveolar value. As such, it has some similarities with the classical ideal alveolar-arterial PO2 gradient. This is obtained by subtracting the PO2 in arterial blood, as measured by the polarographic electrode, from the ideal alveolar PO2. It is important to note that this last value is not actually measured on alveolar gas at all but is a construct obtained from the measured arterial PCO2 and the measured or assumed respiratory exchange ratio.

Arterial PO2. The method of calculating the arterial PO2 from the SpO2 is the means by which we can use the combination of the noninvasive measurement of saturation and the end-tidal values of O2 and CO2 to noninvasively estimate the arterial PO2 and, hence, the oxygen deficit. We use the classical oxygen dissociation curve from Hill with an n value of 2.7 and P50 of 27 mmHg. Calculations using the equation for the oxygen dissociation curve described by Severinghaus (7) have also been carried out, and the results are very similar to those obtained from the Hill equation. The resulting dissociation curve is for a PCO2 of 40 mmHg. To allow for the effect of changes in PCO2 on the oxygen affinity of hemoglobin (Bohr effect), we use the subroutines described by Kelman (4). This procedure assumes no change in the base excess; that is, the change in PCO2 simply moves the arterial point along the normal buffer line. Alterations in base excess will also alter the oxygen affinity of hemoglobin,
but we cannot allow for this. In practice, most patients who are being studied with the Alveolar Gas Meter are likely to have a normal base excess. However, one group that may have an increased base excess will be patients with advanced COPD and chronic CO² retention; calculated arterial PO² will be in error to a small degree in these patients. However, it is worth noting that, in cases in which serial measurements are being made in the same patient, the relative error between measurements will be small.

One difficulty with any oxygen dissociation curve is that, at high PO² values, the curve is so nearly flat that the accuracy of predicting the PO² from the oxygen dissociation curve limits its use to when the SPo² is 95% or less. We based this limit on sensitivity analyses in which we determined the error in calculated PO² that would result from an error in SPo² of ±1 percentage unit. This corresponds to a subsequent uncertainty in calculated PO² of approximately ±5 mmHg. Given that a SPo² of greater than 95% suggests well-preserved gas exchange, we do not consider the magnitude of this error in PO² troubling. At SPo² values of 96% and above, the flat upper portion of the O₂-Hb dissociation curve makes for errors in PO² so large that we consider them unreliable. It is, however, worth noting that at lower values of SPo², the error in PO₂ is smaller, being in the vicinity of ±3mmHg at a SPo² of 90%. This restriction on an upper limit for SPo² will not limit its use in patients with hypoxemia.

Arterial PCO². As was the case with the arterial PO², measuring the arterial PCO² was not a primary objective of this project. However, this number, as obtained from a capnograph, has been shown to be useful in identifying hypoventilation or hyperventilation and in detecting CO² retention in patients with COPD. Also, we use this number to calculate the effect of the PCO² on the oxygen affinity of hemoglobin (Bohr effect).

The Alveolar Gas Meter uses the end-tidal PCO² as a measure of the arterial value. The relation between end-tidal and arterial values has been studied for over 100 years, and a number of studies have shown that in normal subjects the end-tidal value is a close approximation to the arterial PCO² (2). However, the situation in disease is more complicated. In the presence of ventilation-perfusion ratio inequality, the expired PCO² continues to rise during expiration. Two factors contribute to this. First, CO₂ is continually added to the alveolar gas during expiration because of metabolic production. Additionally, in the presence of ventilation/perfusion ratio inequality, units with low ventilation/perfusion ratios tend to empty last, and since these have a higher PCO² than the rest of the lung, the end-tidal PCO² also rises.

Nevertheless, as Fig. 4 shows, the relation between the PCO² in end-tidal gas and that measured using blood gas electrodes is approximately linear. The Bland-Altman analysis shown in Fig. 5 indicates that there is a bias with the measured end-tidal value being 3–4 mmHg less than the value measured with the blood gas electrodes. All but two of the values lie within two standard deviations from the mean, where the standard deviation is ~7 mmHg.

In summary, the great advantages of the noninvasive measurement of impaired gas exchange are its simplicity and ease of measurement. The equipment can be carried by hand to the patient’s bedside, and the actual procedure requires only for the patient to breathe through a tube for 2 or 3 min. The traditional alternative of taking arterial blood is time consuming, potentially uncomfortable for the patient, requires technical skill, and is expensive. Studies to date, including those described in this report, show that this noninvasive technique is very effective at identifying impairment of pulmonary gas exchange. The measurement would be particularly valuable for following the progress of a patient during therapy. Whether the information on the arterial PO² and PCO² provided by the noninvasive technique will be useful in clinical practice has yet to be determined. However, the data suggest that the oxygen deficit derived by the Alveolar Gas Meter provides a useful, noninvasive surrogate measurement of the AaDO² and that this is sensitive to small amounts of disease.

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GRANTS

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DISCLOSURES

The University of California San Diego has exclusively licensed the Alveolar Gas Meter technology to MediPines Corporation, Orange County, CA. J. B. West has a financial interest. None of the other authors has any conflicts of interest, financial, or otherwise, to disclose.

AUTHOR CONTRIBUTIONS


REFERENCES


