A New, Noninvasive Method of Measuring Impaired Pulmonary Gas Exchange in Lung Disease: An Outpatient Study

John B. West, MD, PhD, DSc; Daniel R. Crouch, MD; Janelle M. Fine, BS; Dipen Makadia, BS; Daniel L. Wang, BS; and G. Kim Prisk, DSc

BACKGROUND: It would be valuable to have a noninvasive method of measuring impaired pulmonary gas exchange in patients with lung disease and thus reduce the need for repeated arterial punctures. This study reports the results of using a new test in a group of outpatients attending a pulmonary clinic.

METHODS: Inspired and expired partial pressure of oxygen (PO2) and PCO2 are continually measured by small, rapidly responding analyzers. The arterial PO2 is calculated from the oximeter blood oxygen saturation level and the oxygen dissociation curve. The PO2 difference between the end-tidal gas and the calculated arterial value is called the oxygen deficit.

RESULTS: Studies on 17 patients with a variety of pulmonary diseases are reported. The mean ± SE oxygen deficit was 48.7 ± 3.1 mm Hg. This finding can be contrasted with a mean oxygen deficit of 4.0 ± 0.88 mm Hg in a group of 31 normal subjects who were previously studied (P < .0001). The analysis emphasizes the value of measuring the composition of alveolar gas in determining ventilation-perfusion ratio inequality. This factor is largely ignored in the classic index of impaired pulmonary gas exchange using the ideal alveolar PO2 to calculate the alveolar-arterial oxygen gradient.

CONCLUSIONS: The results previously reported in normal subjects and the present studies suggest that this new noninvasive test will be valuable in assessing abnormal gas exchange in the clinical setting.

KEY WORDS: alveolar-arterial oxygen difference; alveolar gas; alveolar PCO2; alveolar PO2; oxygen dissociation curve

ABBREVIATIONS: PO2 = partial pressure of oxygen; SpO2 = blood oxygen saturation level

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We recently developed a new method for measuring pulmonary gas exchange in patients with lung disease. The patient breathes through a mouthpiece, and a small amount of the gas is continually analyzed by a device that measures the inspired and expired partial pressure of oxygen (PO2) and PCO2. The outputs are available in real time on a screen. The patient also wears an oximeter, and the arterial PO2 is continuously calculated from the blood oxygen saturation level (SpO2) using a formula for the oxygen dissociation curve. We take into account the effect of PCO2 on the curve by using the end-tidal PCO2. The final product, called the oxygen deficit, is obtained by subtracting the calculated arterial PO2 from the end-tidal PO2.

The physiological basis of this new technique has been described elsewhere,1 and recently we reported the results obtained in a series of 31 normal subjects.2 Twenty of the subjects were young, between the ages of 19 and 31 years, and 11 subjects were older, aged between 47 and 88 years. The oxygen deficits of these normal subjects were remarkably small. Specifically, the young subjects had a mean ± SD oxygen deficit of 2.02 ± 3.56 mm Hg. The older subjects had a higher mean oxygen deficit (7.53 ± 5.16 mm Hg). There was a significant difference between the young and old groups.

The present study reports the results of 17 patients attending a pulmonary outpatient clinic of the UC San Diego Health System. These patients are representative of a variety of common lung diseases. The objective was to determine to what extent the oxygen deficit is changed in patients with well-established lung disease.

**Patients and Methods**

The patients attending the clinic were informed of the study, and the measurements were made on all those who volunteered to take part. The procedure was first explained to the patients, and they then signed a consent form approved by the UC San Diego Health institutional review board. The committee name was the Human Research Protection Program, and the project approval number was 160713. The diagnosis was taken from the patient’s chart. Most of the patients had been followed up in the outpatient department for many weeks or even years. Pulmonary function test results supporting the diagnosis were available in the charts.

For the procedure, the patients sat in a chair, and a nose clip was applied; patients were asked to relax and breathe normally through a mouthpiece. A sampling tube was connected from the mouthpiece to a small box that contained the miniature, rapidly responding PO2 and PCO2 sensors and a screen. The result was a continuous analysis of the inspired and expired PO2 and PCO2 (Fig 1). The screen displayed the inspired and expired PAO2 and PACO2 in the upper panel; in the lower panel, the end-tidal values were shown over a longer period of time so that a steady state could be established. In addition, numbers on the screen showed the respiratory frequency, calculated arterial PO2, oxygen deficit, barometric pressure, inspired PO2, heart rate, and SpO2.

Only the results from patients in whom the SpO2 was < 94% were included in this study. The reason for this approach is that when the SpO2 is higher, the oxygen-hemoglobin dissociation curve is so flat that the derivation of calculated arterial PO2 is not accurate. Seventeen patients met this criterion.

The SpO2 was converted to arterial PO2 by using the Hill equation:

\[
\text{PO}_2^n = P_{50}^n \times \left[ \text{SO}_2 / (1 - \text{SO}_2) \right]
\]

where the symbol ^ means raised to the power of, P50 is the PO2 for 50% oxygen saturation assumed to be 27 mm Hg, n is 2.7, and SO2 is the arterial oxygen saturation given by the SpO2. The effect of changes in PCO2 on the oxygen affinity of hemoglobin was taken into account by using the end-tidal PCO2 and employing a Kelm subroutine.3 However, it is not possible to allow for changes in pH caused by alterations in base excess, as discussed previously.1,2

**Results**

Table 1 shows the results for the 17 patients. The columns show an identifier, age, sex, end-tidal PO2, end-tidal PCO2, SpO2, calculated arterial PO2, and the calculated oxygen deficit. The patients have been ordered according to age as in the study of normal subjects. The calculated oxygen deficit yielded a mean ± SD value of 48.7 ± 12.9 mm Hg.

Figure 2 shows the results of a nonpaired t test to determine whether there was a significant difference between the results of the normal subjects and the study patients. The P value for the difference between the two groups was < .0001. This figure emphasizes the large effect of pulmonary disease on the oxygen deficit.
No attempt was made to select patients who had serious disease. The only selection process was whether the patient agreed to take part in the study. If anything, the result of this approach was that patients who were seriously disabled were reluctant to agree, and therefore the results are biased in the direction of patients with less serious disease. As indicated earlier, this report is limited to patients in whom the SpO2 was < 94%. This criterion selected out some patients with minor impairment of gas exchange. All the patients were ambulant.

As expected from a general pulmonary outpatient clinic, there was considerable variety in the diagnoses of the 17 patients. Not surprisingly, the most common diagnosis was COPD, which was reported in 10 patients. Three of the patients had interstitial lung disease, and OSA was diagnosed in five patients. Two of the patients had coronary artery disease, and two patients had rheumatoid arthritis. Other conditions included recovery from pneumonia, pulmonary edema, DVT with the possibility of pulmonary embolism, pleural effusion, hepatic cirrhosis, and cryptogenic organizing pneumonia.

To determine the relative importance of the physiological variables that were responsible for increasing the oxygen deficit, four factors were examined that contribute to this index. The first is the SpO2 because the lower the arterial oxygen saturation, the smaller is the calculated arterial PO2. Next was the arterial PO2 itself. A third factor is the end-tidal PO2 because this factor minus the calculated arterial PO2. Finally, the end-tidal PCO2 was examined because this measure is used to take account of the effect of the PCO2 on the oxygen affinity of hemoglobin, and thus the position of the oxygen dissociation curve.
small effect of the SpO₂ on the oxygen deficit is surprising because the oximeter reading is frequently relied on in clinical practice to guide therapy (eg, weaning from a ventilator).

The second factor is the calculated arterial PO₂. Not surprisingly, this factor has a large influence on the oxygen deficit because the deficit is calculated from the end-tidal PO₂ minus the calculated arterial PO₂. As Figure 3 shows, the effect of the calculated arterial PO₂ on the oxygen deficit is much greater than that of the SpO₂, the $R^2$ values being 0.67 and 0.22, respectively.

Another unexpected feature of these plots is the great importance of the third factor, end-tidal PCO₂. The influence of this factor is greater than either the arterial oxygen saturation or the calculated arterial PO₂. The end-tidal PO₂ is the number from which the calculated arterial PO₂ is subtracted to derive the oxygen deficit. However, it is remarkable that the end-tidal value is so important, and the implications of this outcome are discussed further later in the text.

Finally, it was also surprising that the fourth factor, the end-tidal PCO₂, turned out to be so significant, with an $R^2$ value of 0.698. This finding must mean that the influence of the PCO₂ on the position of the oxygen dissociation curve plays a major role in the calculation of the arterial PO₂.

In summary, if we use the $R^2$ values as a measure of the importance of the four factors influencing the oxygen deficit, the order of importance is end-tidal PO₂, end-tidal PCO₂, calculated arterial PO₂, and finally arterial oxygen saturation.

### TABLE 1  | Results for the 17 Outpatients

<table>
<thead>
<tr>
<th>ID</th>
<th>Age, y</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>PETO₂</th>
<th>PETCO₂</th>
<th>SpO₂</th>
<th>Calc PaO₂</th>
<th>Oxygen Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>49</td>
<td>M</td>
<td>COPD, severe OSA</td>
<td>108</td>
<td>41</td>
<td>90</td>
<td>60</td>
<td>47</td>
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<tr>
<td>29</td>
<td>54</td>
<td>M</td>
<td>ILD, respiratory failure</td>
<td>89</td>
<td>44</td>
<td>91</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>64</td>
<td>54</td>
<td>M</td>
<td>ILD</td>
<td>120</td>
<td>26</td>
<td>88</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
<td>F</td>
<td>Recovering pneumonia, CAD, RA</td>
<td>116</td>
<td>30</td>
<td>91</td>
<td>56</td>
<td>61</td>
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<tr>
<td>40</td>
<td>60</td>
<td>F</td>
<td>COPD, previous DVT and PE, possible OSA</td>
<td>114</td>
<td>40</td>
<td>93</td>
<td>66</td>
<td>48</td>
</tr>
<tr>
<td>31</td>
<td>61</td>
<td>M</td>
<td>COPD, OSA, HTN, ischemic heart disease</td>
<td>110</td>
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<td>51</td>
</tr>
<tr>
<td>61</td>
<td>61</td>
<td>M</td>
<td>COPD, respiratory failure, HYP, OSA, ILD</td>
<td>114</td>
<td>31</td>
<td>90</td>
<td>61</td>
<td>52</td>
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<tr>
<td>42</td>
<td>62</td>
<td>F</td>
<td>COPD, RA</td>
<td>113</td>
<td>30</td>
<td>92</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td>62</td>
<td>64</td>
<td>M</td>
<td>COPD</td>
<td>111</td>
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<tr>
<td>41</td>
<td>65</td>
<td>F</td>
<td>COPD</td>
<td>112</td>
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<td>93</td>
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<tr>
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<td>96</td>
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<td>68</td>
<td>27</td>
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<tr>
<td>35</td>
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<td>F</td>
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<td>93</td>
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<td>43</td>
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<td>F</td>
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<td>63</td>
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<tr>
<td>57</td>
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<td>M</td>
<td>ILD, OSA, CAD, HTN</td>
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<td>86</td>
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<td>76</td>
<td>F</td>
<td>Pulmonary edema, leukemia, pneumonia, PE, CHF</td>
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<td>40</td>
<td>87</td>
<td>54</td>
<td>48</td>
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<tr>
<td>49</td>
<td>79</td>
<td>M</td>
<td>COPD, OSA, previous lung cancer and PE, HTN</td>
<td>102</td>
<td>44</td>
<td>91</td>
<td>65</td>
<td>37</td>
</tr>
<tr>
<td>Mean</td>
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<td></td>
<td></td>
<td>110</td>
<td>36</td>
<td>91</td>
<td>61</td>
<td>49</td>
</tr>
</tbody>
</table>

The columns show an identifier, age, sex, diagnosis, end-tidal partial pressure of oxygen (PETO₂), end-tidal PCO₂ (PETCO₂), blood oxygen saturation level (SpO₂), calculated PaO₂, and oxygen deficit. The mean oxygen deficit was 49 mm Hg; the SD was 13 mm Hg. BOOP = bronchiolitis obliterans with organizing pneumonia; CAD = coronary artery disease; Calc = calculated; CHF = congestive heart failure; COPO₂ = cryptogenic organizing pneumonia; F = female; HTN = hypertension; ILD = interstitial lung disease; M = male; PE = pulmonary embolism; RA = rheumatoid arthritis.
Discussion

The most important finding of the present study is that this new index of impaired gas exchange, the oxygen deficit, seems to be very sensitive in detecting abnormal lung function. This finding is emphasized in Figure 2, where the difference between the outpatients and a group of normal subjects is so striking. This outcome is consistent with the results of our previous study of normal subjects, in which we found a significant difference between the oxygen deficits of young and old subjects despite the fact that the latter had no evidence of lung disease.2 Because the measurement of oxygen deficit is made noninvasively without the necessity of sampling arterial blood, it may be of considerable clinical value. Although we initially chose to study patients with well-established disease as would typically be seen in an outpatient clinic, it will now be important to look at patients with early disease.

Because the test is noninvasive, and only takes a few minutes to perform, it may be particularly valuable in following the progress of a patient with lung disease who is undergoing treatment. A possible scenario is that a patient is admitted to the hospital with pulmonary disease that requires a full investigation to be certain of the diagnosis and to look for comorbidities. It is probable that this patient will require an analysis of arterial blood gases because this test is the traditional gold standard for measuring impairment of gas exchange. However, after the initial evaluation, the progress of the patient as a result of therapy might be adequately managed by using this noninvasive test. Because it is simple to perform and takes only a few minutes, the test could be frequently repeated to monitor the changes in pulmonary gas exchange.

An important finding here is the great value of sampling alveolar gas. From the earliest days of analyzing pulmonary gas exchange, it has always been emphasized that an important step is the movement of oxygen from the alveolar gas to the arterial blood.4,5 The arterial PO2 was available from a sample of blood. However, finding an index for alveolar gas was a challenge. Riley and Cournand4 introduced the notion of ideal alveolar gas. This was the composition that the alveolar gas would have if there were no ventilation-perfusion inequality in the lung and the lung exchanged gas with the same respiratory exchange ratio as existed at the time.

As a result, the Riley analysis has now been in use for some 70 years. It involves sampling arterial blood, using the arterial PCO2 as a measure of the Pco2 in ideal alveolar gas, measuring or assuming the respiratory exchange ratio, and inserting these values into the
alveolar gas equation. The result is referred to as the alveolar-arterial gradient or difference, where the alveolar value is that of ideal alveolar gas. This procedure is used extensively in clinical practice. It is noteworthy that alveolar gas itself is not sampled, and the ideal alveolar gas is simply a construct based on the arterial P\(_{CO_2}\).

The results reported here, however, question whether this process accurately measures gas exchange in the whole lung. Figure 4 shows a classic oxygen-CO\(_2\) diagram with the ventilation-perfusion ratio line. This line joins the point for mixed venous blood to that for inspired gas, and it shows the gas composition of all lung units from a ventilation-perfusion ratio of zero to one that is infinitely high. The ideal alveolar gas point is found where the line for the existing respiratory exchange ratio intersects with the ventilation-perfusion ratio line.

Figure 4 also shows that only a portion of the lung units undergoing gas exchange is represented by the classic Riley analysis. These are the lung units to the left of the ideal alveolar gas point; they are the lung units with abnormally low ventilation-perfusion ratios. The lung units represented by the ventilation-perfusion ratio line that is located to the right of the ideal alveolar value are not taken into account. The result is that the Riley analysis is markedly biased by lung units with abnormally low ventilation-perfusion ratios. The new analysis that results in the oxygen deficit is very different. The alveolar gas value is not represented by the ideal point but by the end-tidal gas.

An important issue is how repeatable these measurements are for the end-tidal PO\(_2\) and P\(_{CO_2}\). It is known that the PO\(_2\) falls and the P\(_{CO_2}\) rises as expiration proceeds because poorly ventilated lung units empty last. We have studied this issue in detail and believe that highly reproducible measurements of end-tidal PO\(_2\) and P\(_{CO_2}\) can be achieved if the patient is in a steady state. This approach involves confirming that the expiratory volume is strictly repeatable so that the last expired gas comes from the lung at functional residual capacity, or a volume just above this level. The functional residual capacity is a fundamental property of the lung because it is the volume at which the inward recoil of the lung and the outward spring of the chest wall are equal. The tracing in Figure 1 shows that the end-tidal values are highly reproducible if a steady state is achieved. Furthermore, a tracing such as that shown in Figure 1 is very sensitive to changes in both the respiratory rate and tidal volume. An increase or decrease in rate can immediately be recognized by the frequency of the expiratory gas changes, and the expiratory volume can also be accurately monitored because an abnormally small volume results in a reduced deflection, whereas an abnormally high volume results in a large deflection. Therefore, close attention can be given to achieving a steady state, and the result is that the end-tidal PO\(_2\) and P\(_{CO_2}\) can be acceptably reproducible.

![Figure 4 – Classic oxygen-CO\(_2\) diagram with the ventilation-perfusion line joining the points for mixed venous blood and inspired gas. The traditional Riley analysis is based on the composition of arterial blood and ideal alveolar gas, and it is strongly biased by lung units with low ventilation-perfusion ratios that lie to the left of the ideal point. By contrast, the new test also includes contributions from lung units with high ventilation-perfusion ratios that are located to the right of the ideal point. Details are discussed in the text. See Figure 1 legend for expansion of abbreviations.](image-url)
It is noteworthy that the values of the PO2 and PCO2 obtained from arterial puncture suffer from the same difficulties. If the tidal volume is altered, or the frequency changes during the removal of the blood sample, both the PO2 and PCO2 will change, although we accept these inaccuracies in practice.

This analysis shows why the end-tidal PO2 is so powerful in contributing to the oxygen deficit as shown in Figure 3. It also explains the importance of the end-tidal PCO2 because this factor apparently has a major role in determining the position of the oxygen dissociation curve, and thus the value of the calculated arterial PO2. Finally, the weak contribution to the oxygen deficit made by the SpO2 is also explained. This factor takes no account of the effects of ventilation-perfusion inequality except its influence in reducing the arterial oxygen saturation.

The new index emphasizes the importance of ventilation-perfusion inequality on the composition of alveolar gas. This factor is essentially ignored in the Riley analysis, and its importance is often not understood. However, when ventilation-perfusion inequality is imposed on a theoretical lung that has uniform ventilation and blood flow, two separate events occur. One is that there is a fall in arterial PO2 and a rise in arterial PCO2, although the latter may not be seen because the tendency for the PCO2 to rise is negated by its effect on increasing the alveolar ventilation. However, it is not generally appreciated that at the same time the ventilation-perfusion inequality raises the alveolar PO2 and reduces the alveolar PCO2. These changes are not reflected in the analysis based on ideal alveolar gas but do contribute to the oxygen deficit.

Conclusions

This new, noninvasive method of measuring impaired gas exchange in patients with lung disease is very sensitive to the presence of disease and may obviate the need for arterial punctures in many instances.

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References