CHEST

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 (PO_2) and P_{CO_2} are continually measured by small, rapidly responding analyzers. The arterial PO_2 is calculated from the oximeter blood oxygen saturation level and the oxygen dissociation curve. The PO_2 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 $\pm$ SE oxygen deficit was 48.7 $\pm$ 3.1 mm Hg. This finding can be contrasted with a mean oxygen deficit of 4.0 $\pm$ 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 PO_2 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.
CHEST 2018; 154(2):363-369

KEY WORDS: alveolar-arterial oxygen difference; alveolar gas; alveolar PCO_2; alveolar PO_2; oxygen dissociation curve

---

ABBREVIATIONS: PO_2 = partial pressure of oxygen; SpO_2 = blood oxygen saturation level

AFFILIATIONS: From the Department of Medicine (Drs West, Crouch, and Prisk; Ms Fine; and Mr Wang), University of California San Diego, La Jolla, CA; and MediPines Corporation (Mr Makadia), Newport Beach, CA.

FUNDING/SUPPORT: Financial support was provided by the University of California San Diego, and they have licensed MediPines Corporation to develop the study device.

CORRESPONDENCE TO: John B. West, MD, PhD, DSc, UCSD Department of Medicine, 0623A, 9500 Gilman Dr, La Jolla, CA 92093; e-mail: jwest@ucsd.edu

DOI: https://doi.org/10.1016/j.chest.2018.02.001

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 (PO_2) and P_{CO_2}. The outputs are available in real time on a screen. The patient also wears an oximeter, and the arterial PO_2 is continuously calculated from the blood oxygen saturation level (SpO_2) using a formula for the oxygen dissociation curve. We take into account the effect of P_{CO_2} on the curve by using the end-tidal P_{CO_2}. The final product, called the oxygen deficit, is obtained by subtracting the calculated arterial PO_2 from the end-tidal PO_2.

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 $\pm$ SD oxygen deficit of 2.02 $\pm$ 3.56 mm Hg. The older subjects had a higher mean oxygen deficit (7.53 $\pm$ 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 PO_2 and P_{CO_2} sensors and a screen. The result was a continuous analysis of the inspired and expired PO_2 and P_{CO_2} (Fig 1). The screen displayed the inspired and expired P_{AO_2} and P_{ACO_2} 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 PO_2, oxygen deficit, barometric pressure, inspired PO_2, heart rate, and SpO_2.

Only the results from patients in whom the SpO_2 was < 94% were included in this study. The reason for this approach is that when the SpO_2 is higher, the oxygen-hemoglobin dissociation curve is so flat that the derivation of calculated arterial PO_2 is not accurate. Seventeen patients met this criterion.

The SpO_2 was converted to arterial PO_2 by using the Hill equation:

$$PO_2\hat{}n = P_{50}\hat{}n \times \left[SO_2 /(1 - SO_2)\right]$$

where the symbol ^ means raised to the power of, P_{50} is the PO_2 for 50% oxygen saturation assumed to be 27 mm Hg, n is 2.7, and SO_2 is the arterial oxygen saturation given by the SpO_2. The effect of changes in P_{CO_2} on the oxygen affinity of hemoglobin was taken into account by using the end-tidal P_{CO_2} and employing a Kelman 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 PO_2, end-tidal P_{CO_2}, SpO_2, calculated arterial PO_2, 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 $\pm$ SD value of 48.7 $\pm$ 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.

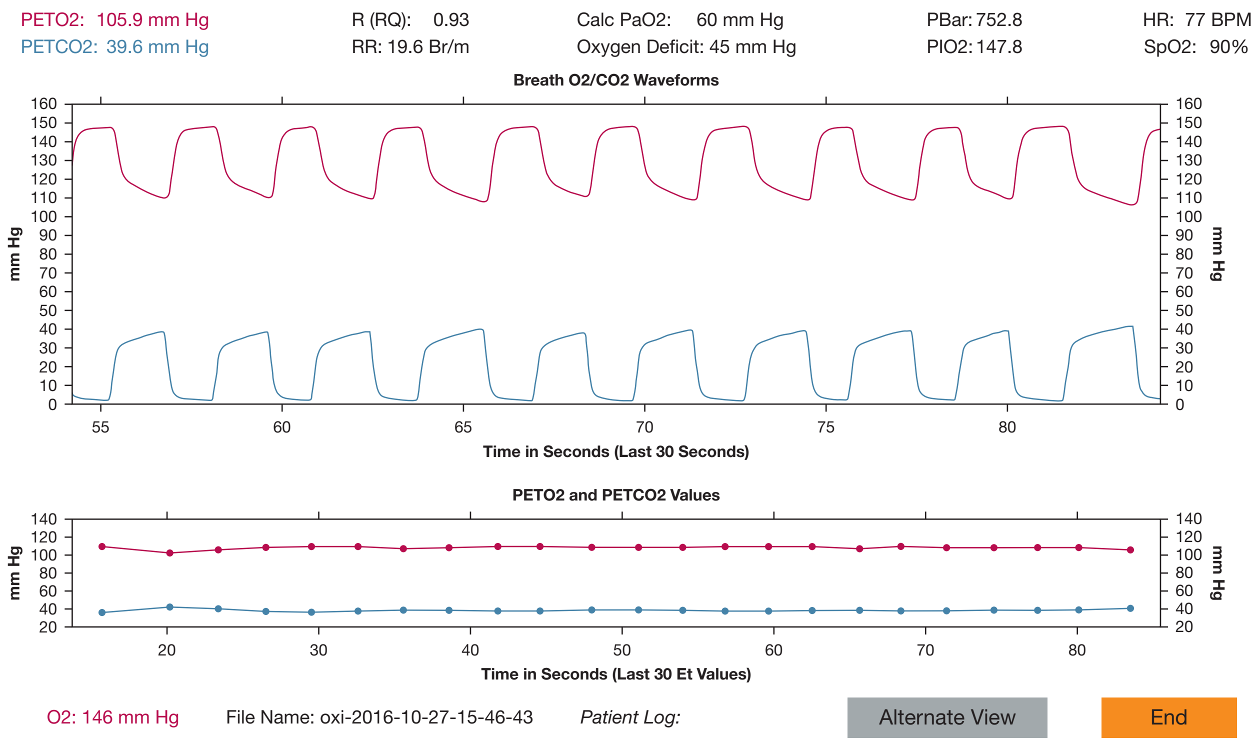

Figure 1 – *Example of a screenshot of the output of the device for a patient with COPD and OSA. Note the continuous records of inspired and expired PO_2 (red) and PCO_2 (blue). Below these are plots of the end-tidal PO_2 and PCO_2 for a larger number of breaths to show whether the subject is in a steady state. The display also reads out the end-tidal PO_2 and PCO_2 values, RR, calculated arterial PO_2, oxygen deficit, HR, SpO_2, PBar, and inspired PO_2. HR = heart rate; PBar = barometric pressure; $PETCO_2$ = end-tidal CO_2 pressure; $PETO_2$ = end-tidal partial pressure of oxygen; PO_2 = partial pressure of oxygen; RR = respiratory rate; SpO_2 = blood oxygen saturation level.*

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 SpO_2 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 SpO_2 because the lower the arterial oxygen saturation, the smaller is the calculated arterial PO_2. Next was the arterial PO_2 itself. A third factor is the end-tidal PO_2 because the oxygen deficit is determined by this factor minus the calculated arterial PO_2. Finally, the end-tidal PCO_2 was examined because this measure is used to take account of the effect of the PCO_2 on the oxygen affinity of hemoglobin, and thus the position of the oxygen dissociation curve.

Figure 3 displays plots of the oxygen deficit against each of these four factors, and the results were surprising. First, the arterial oxygen saturation had the smallest effect of all four factors on the oxygen deficit as judged by the R^2 value. This outcome was unexpected and presumably means that the other factors which determine the derivation of the arterial PO_2 from the oxygen saturation are very important. The chief of these is the arterial PCO_2 because this factor influences the position of the oxygen dissociation curve. The relatively

TABLE 1] Results for the 17 Outpatients

ID	Age, y	Sex	Diagnosis	$PETO_2$	$PETCO_2$	SpO_2	Calc PaO_2	Oxygen Deficit
27	49	M	COPD, severe OSA	108	41	90	60	47
29	54	M	ILD, respiratory failure	89	44	91	65	24
64	54	M	ILD	120	26	88	50	70
30	60	F	Recovering pneumonia, CAD, RA	116	30	91	56	61
40	60	F	COPD, previous DVT and PE, possible OSA	114	40	93	66	48
31	61	M	COPD, OSA, HTN, ischemic heart disease	110	38	90	59	51
61	61	M	COPD, respiratory failure, HYP, OSA, ILD	114	31	90	61	52
42	62	F	COPD, RA	113	30	92	61	52
62	64	M	COPD	111	30	93	64	47
41	65	F	COPD	112	34	93	66	46
67	69	M	COPD	96	50	92	68	27
35	70	F	Respiratory failure, pleural effusion, OSA	108	36	93	67	40
43	73	F	COPD, BOOP, recovering cold	104	39	91	63	42
57	74	M	ILD, OSA, CAD, HTN	119	31	86	48	71
34	76	F	Pulmonary edema, leukemia, pneumonia, PE, CHF	102	40	87	54	48
52	78	M	ILD, previous TB	123	27	92	59	64
49	79	M	COPD, OSA, previous lung cancer and PE, HTN	102	44	91	65	37
Mean				110	36	91	61	49

The columns show an identifier, age, sex, diagnosis, end-tidal partial pressure of oxygen ($PETO_2$), end-tidal P_{CO_2} ($PETCO_2$), blood oxygen saturation level (SpO_2), calculated PaO_2, 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; COP = cryptogenic organizing pneumonia; F = female; HTN = hypertension; ILD = interstitial lung disease; M = male; PE = pulmonary embolism; RA = rheumatoid arthritis.

small effect of the SpO_2 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 PO_2. Not surprisingly, this factor has a large influence on the oxygen deficit because the deficit is calculated from the end-tidal PO_2 minus the calculated arterial PO_2. As

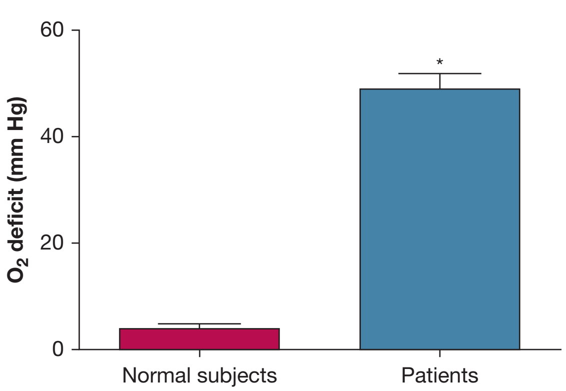

Figure 2 – *Results of a nonpaired* t *test comparing the 17 study patients and 31 normal subjects from a previous study.*[2] *Means and SEs are shown. Note the large difference between the two groups.* *P < .0001.

Figure 3 shows, the effect of the calculated arterial PO_2 on the oxygen deficit is much greater than that of the SpO_2, 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 PO_2. The influence of this factor is greater than either the arterial oxygen saturation or the calculated arterial PO_2. The end-tidal PO_2 is the number from which the calculated arterial PO_2 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 P_{CO_2}, turned out to be so significant, with an R^2 value of 0.698. This finding must mean that the influence of the P_{CO_2} on the position of the oxygen dissociation curve plays a major role in the calculation of the arterial PO_2.

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 PO_2, end-tidal P_{CO_2}, calculated arterial PO_2, and finally arterial oxygen saturation.

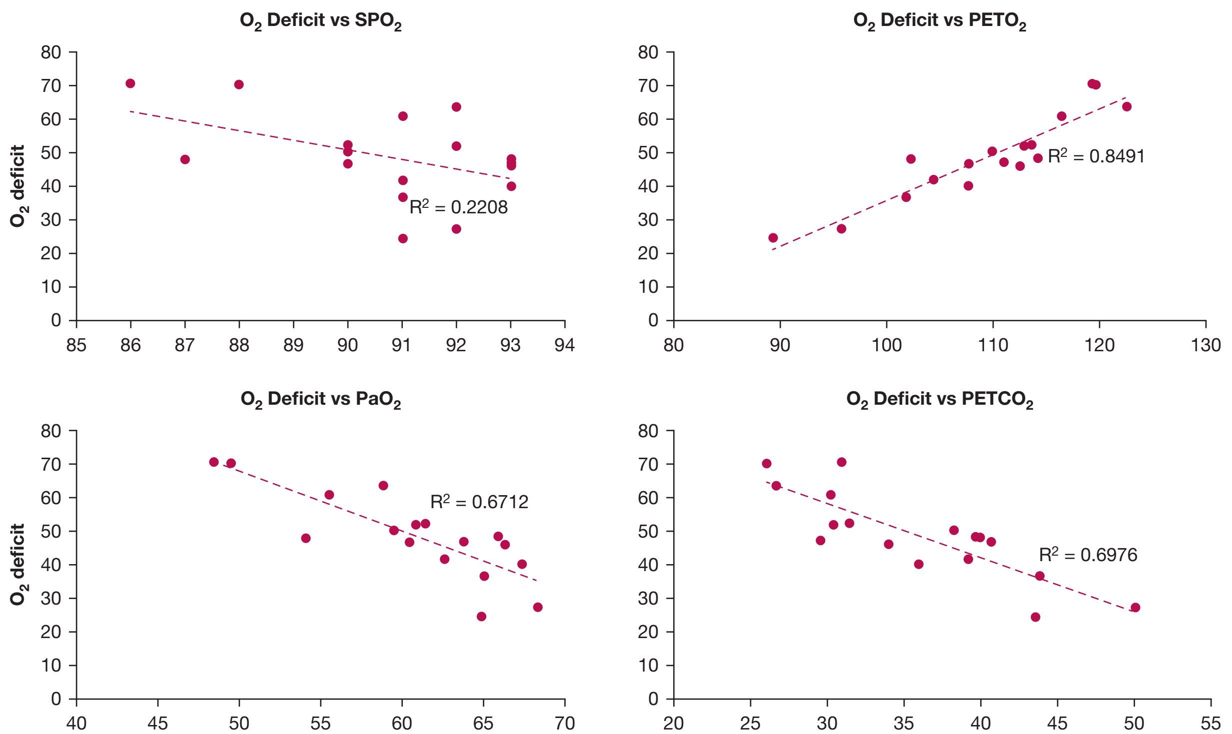

Figure 3 – *Plots of the oxygen deficit against each of the four factors that determine it. The four factors are the* SpO_2*, the calculated* PaO_2*, the end-tidal* PO_2*, and the end-tidal* P_{CO_2}*. Details are discussed in the text.* O_2 *= oxygen. See Figure 1 legend for expansion of abbreviations.*

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 PO_2 was available from a sample of blood. However, finding an index for alveolar gas was a challenge. Riley and Cournand[4] 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 P_{CO_2} as a measure of the P_{CO_2} 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.[6] 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.

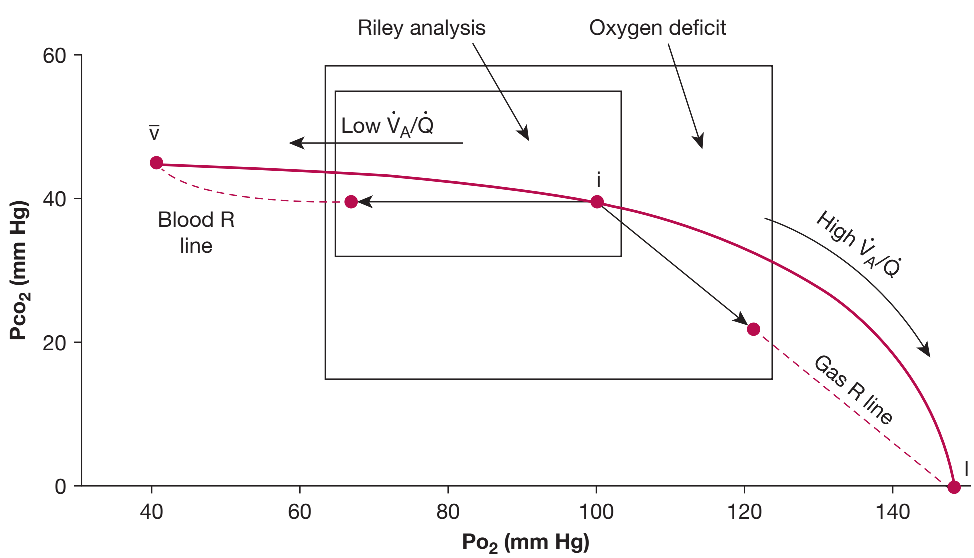

Figure 4 – *Classic oxygen-CO_2 diagram with the ventilation-perfusion line joining the points for mixed venous blood and inspired gas. The traditional Riley analysis is based on the composition of arterial blood and ideal alveolar gas, and it is strongly biased by lung units with low ventilation-perfusion 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.*

It is noteworthy that the values of the PO_2 and PCO_2 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 PO_2 and PCO_2 will change, although we accept these inaccuracies in practice.

This analysis shows why the end-tidal PO_2 is so powerful in contributing to the oxygen deficit as shown in Figure 3. It also explains the importance of the end-tidal PCO_2 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 PO_2. Finally, the weak contribution to the oxygen deficit made by the SpO_2 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.[7] One is that there is a fall in arterial PO_2 and a rise in arterial PCO_2, although the latter may not be seen because the tendency for the PCO_2 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 PO_2 and reduces the alveolar PCO_2. 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.

Acknowledgments

Author contributions: J. B. W., D. R. C., D. L. W., and G. K. P. were responsible for the conception and design of the study; J. B. W., J. M. F., D.M., D. L. W., and G. K. P. were responsible for the analysis and interpretation of the results; and J. B. W., D. R. C., J. M. F., D. L. W., and G. K. P. were responsible for drafting of the manuscript and for important intellectual contributions.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: J. B. W. has a financial interest in MediPines Corporation. None declared (D. R. C., J. M. F., D. M., D. L. W., G. K. P.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors thank Esteban A. Moya, PhD, and Zhenxing Fu, PhD, for help with the statistics and figures.

References

1. West JB, Prisk GK. A new method for noninvasive measurement of pulmonary gas exchange using expired gas. *Resp Physiol Neuro Biol*. 2018;247:112-115.
2. West JB, Wang DL, Prisk GK. Measurements of pulmonary gas exchange efficiency using expired gas and oximetry: results in normal subjects. *Am J Physiol Lung Cell Mol Physiol*. 2018;314(4):L686-L689.
3. Kelman CR. Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol*. 1966;21(4):1375-1376.
4. Riley RL, Cournand A. "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. *J Appl Physiol*. 1949;1(12):825-847.
5. Rahn H, Fenn WO. *A Graphical Analysis of the Respiratory Gas Exchange: the O_2–CO_2 Diagram*. Washington, DC: The American Physiological Society; 1955.
6. Fowler WS. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J Appl Physiol*. 1949;2(6):283-299.
7. West JB. Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Resp Physiol*. 1969;7(1):88-110.