Am J Physiol Lung Cell Mol Physiol 314: L686–L689, 2018.
First published December 20, 2017; doi:10.1152/ajplung.00499.2017.

RESEARCH ARTICLE

Measurements of pulmonary gas exchange efficiency using expired gas and oximetry: results in normal subjects

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Submitted 15 November 2017; accepted in final form 17 December 2017

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* 314: L686–L689, 2018. First published December 20, 2017; doi:10.1152/ajplung.00499.2017.—We are developing a novel, noninvasive method for measuring the efficiency of pulmonary gas exchange in patients with lung disease. The patient wears an oximeter, and we measure the partial pressures of oxygen and carbon dioxide in inspired and expired gas using miniature analyzers. The arterial P_{O_2} is then calculated from the oximeter reading and the oxygen dissociation curve, using the end-tidal P_{CO_2} to allow for the Bohr effect. This calculation is only accurate when the oxygen saturation is <94%, and therefore, these normal subjects breathed 12.5% oxygen. When the procedure is used in patients with hypoxemia, they breathe air. The P_{O_2} difference between the end-tidal and arterial values is called the "oxygen deficit." Preliminary data show that this index increases substantially in patients with lung disease. Here we report measurements of the oxygen deficit in 20 young normal subjects (age 19 to 31 yr) and 11 older normal subjects (47 to 88 yr). The mean value of the oxygen deficit in the young subjects was 2.02 ± 3.56 mmHg (means ± SD). This mean is remarkably small. The corresponding value in the older group was 7.53 ± 5.16 mmHg (means ± SD). The results are consistent with the age-related trend of the traditional alveolar-arterial difference, which is calculated from the calculated ideal alveolar P_{O_2} minus the measured arterial P_{O_2}. That measurement requires an arterial blood sample. The present study suggests that this noninvasive procedure will be valuable in assessing the degree of impaired gas exchange in patients with lung disease.

alveolar-arterial oxygen difference; alveolar gas; alveolar P_{CO_2}; alveolar P_{O_2}; oxygen dissociation curve

INTRODUCTION

The traditional way of measuring impaired gas exchange in patients with pulmonary disease has been to use arterial blood gases. However, obtaining an arterial blood sample has some disadvantages. It requires a technically skilled operator, may be uncomfortable for the patient, occasionally causes complications, and is expensive. For these reasons, we have recently been developing a noninvasive method of measuring impaired pulmonary gas exchange (8). The patient breathes into a device that measures the P_{O_2} and P_{CO_2} of expired gas. In addition, the patient wears a pulse oximeter, and we calculate the arterial P_{O_2} from the oximeter reading and the oxygen dissociation curve, taking into account the Bohr effect by using the end-tidal P_{CO_2}. The difference between the end-tidal alveolar and arterial P_{O_2} is referred to as the "oxygen deficit." In a preliminary series of measurements on outpatients in a pulmonary clinic, we have found that the oxygen deficit is substantially raised in patients with lung disease (9).

This new index has similarities with the traditional ideal alveolar-arterial oxygen difference that is frequently employed to assess the efficiency of gas exchange. That difference is calculated using the measured arterial P_{CO_2} and the measured or assumed respiratory exchange ratio and then employing the alveolar gas equation. The disadvantages of this traditional index include the fact that it requires an arterial blood sample. In addition, its magnitude is strongly influenced by the contribution of lung units with low ventilation-perfusion ratios whereas, as discussed below, the new index gives a more comprehensive measure of gas exchange efficiency. A detailed analysis of how the new oxygen deficit index is related to the traditional alveolar-arterial (A-a) oxygen difference has been published (8).

The purpose of the present study was to determine normal values for the oxygen deficit in young normal subjects and also to see if this was influenced by age. The reason for looking at age is that the traditional A-a difference is known to increase with age, presumably because the aging lung becomes less efficient at gas exchange. Here we present results on 20 young normal subjects and 11 older people without lung disease.

METHODS

The subjects were students, staff, and faculty at the Univeristy of California, San Diego, who volunteered. The procedure was first explained to them, and they then signed the consent form approved by the Univeristy of California, San Diego Institutional Review Board. First, the subjects were asked about pulmonary symptoms or other evidence of lung disease. Then, spirometry was carried out including measurements of the forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the FEV/FVC percent. Only subjects who denied symptoms of lung disease and who had normal spirometry were accepted.

For the main procedure the subjects sat in a comfortable chair in a semirecumbent posture, a nose clip was applied, and they 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 P_{O_2} and P_{CO_2} sensors and a screen. The result was a continuous analysis of the inspired and expired P_{O_2} and P_{CO_2}.

Because we were studying normal subjects with O_2 saturations >95% breathing air, to make these measurements we used a hypoxic gas mixture to lower their arterial oxygen saturation so that the O_2 deficit could be reliably measured (8). After a few minutes of breathing air during which a steady state was obtained, the subject was

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connected to a bag containing 12.5% oxygen in nitrogen via a low resistance nonrebreathing valve. This provided an inspired P_{O_2} of ~90 mmHg. This value was chosen to match the P_{O_2} in the air at the University of California, Barcroft high-altitude laboratory, altitude of 3,800 m, a hypoxic exposure used extensively by our group in the past. After a steady state of gas exchange had been established as shown in Fig. 1, the subject was connected again to room air and the final set of data was obtained.

The subject wore an oximeter probe on one finger, and the SpO_2 was continually displayed as shown in Fig. 1, *top*. The time taken for the SpO_2 to fall from its normal value of ~97% to its steady-state value breathing the hypoxic mixture was ~1–2 min. When normoxic breathing was reestablished, the SpO_2 rapidly rose to its previous value during air breathing. As Fig. 1 shows, the end-tidal values of P_{O_2} and P_{CO_2} were readily available from the display. In practice, the software averaged the end-tidal P_{O_2} values for the preceding five breaths, and these numbers were displayed over a longer period to determine whether a steady state had been established. This tracing is seen in Fig. 1, *bottom*.

The SpO_2 was converted to arterial P_{O_2} using the Hill equation $(P_{O_2})^n = (P_{50})^n \times [S_{O_2}/(1 - S_{O_2})]$, where P_{50} is the P_{O_2} for 50% oxygen saturation assumed to be 27 mmHg, n is 2.7, and S_{O_2} is the arterial oxygen saturation given by the SpO_2. The effects of changes in P_{CO_2} on the oxygen affinity of hemoglobin were taken into account by using the end-tidal P_{CO_2} and employing a Kelman subroutine (3).

The reason for using the hypoxic inspired gas is that the calculations from the oxygen dissociation curve are inaccurate above an SpO_2 of ~93% because the curve is so flat. This was clearly seen in the data during air breathing where the calculated arterial P_{O_2} showed large variations. By contrast, the calculated arterial P_{O_2} during hypoxia showed less variation.

Comparisons between groups (young/old) were performed using an unpaired t-test with significance accepted at $P < 0.05$, two-tailed. Least-squares linear regression was used to describe the effect of age on O_2 deficit.

RESULTS

Table 1 shows the results for the 20 young normal subjects in the first part and for 11 older normal subjects in the second part. The columns show an identifier, age, sex, end-tidal P_{O_2}, end-tidal P_{CO_2}, SpO_2, calculated arterial P_{O_2}, and the calculated oxygen deficit. In both parts of the table, the subjects have been ordered by age. Note that in the first part, the age varied from 19 to 31 yr and in the second part from 47 to 88 yr. Only the data for hypoxic breathing, that is 12.5% oxygen, are shown. Note that for the young subjects, the calculated oxygen deficit had a mean value of 2.02 mmHg with the SD of 3.56 mmHg with an approximately normal distribution. For the older subjects, the mean is 7.53 mmHg with a SD of 5.16 mmHg. Spirometry was normal with the means ± SD% for the FEV_1/FVC being 101.6 ± 10.3 in the young group and 102.4 ± 8.0 in the older group. Note that some subjects hyperventilated as evidenced by a reduced arterial P_{CO_2}, and this reduces the oxygen deficit. In cases in which the oxygen deficit is very low, an occasional negative number results (Table 1) as expected given a modest degree of scatter in the measurements used to calculate the index. Figure 2 shows a plot of the oxygen deficit against age with the linear least-squares line of best fit. The difference in O_2 deficit between the two groups is shown in Fig. 3 with $P = 0.0015$. The increase of the oxygen deficit with age is consistent with the results reported by others (4, 5). Figure 3 also emphasizes the small value of the mean in the young normal group.

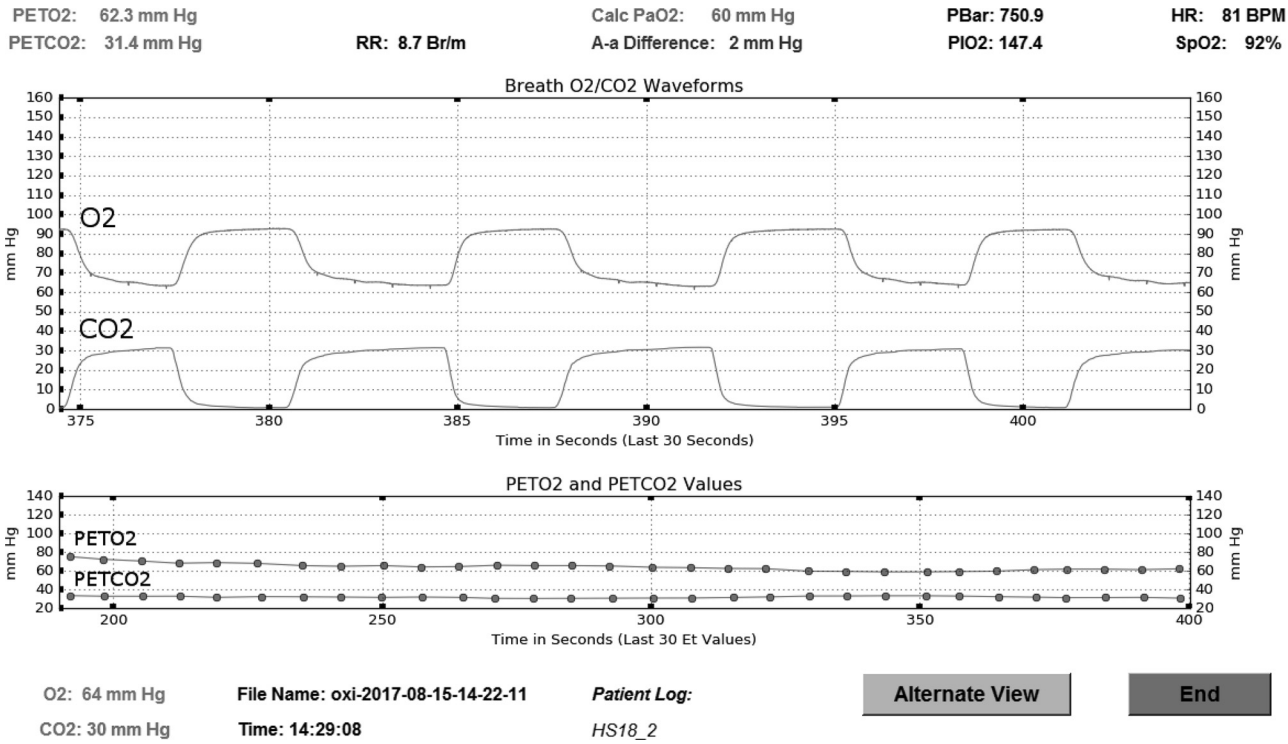

Fig. 1. Typical screenshot of the output of the device for a normal subject while breathing 12.5% oxygen. Note the continuous records of inspired and expired P_{O_2} and P_{CO_2}. *Bottom*: plots of the end-tidal P_{O_2} and P_{CO_2} for a larger number of breaths to show whether the subject is in a steady state. The display also reads out the end-tidal P_{O_2} and P_{CO_2} values, respiratory rate, calculated arterial P_{O_2}, difference between the end-tidal and calculated arterial P_{O_2} (oxygen deficit), heart rate, SpO_2, barometric pressure, and inspired P_{O_2}. RR, respiratory rate; A-a, alveolar-arterial difference; HR, heart rate; PIO_2, inspired P_{O_2}; PBar, barometric pressure.

Table 1. *Results for the 20 young normal subjects and 11 older normal subjects*

	Age	Sex	PET_{O_2}	PET_{CO_2}	SpO_2	$CalcPa_{O_2}$	O_2 Deficit
Normal subjects							
HS05	19	M	72	26.9	95	70	2
HS22	22	M	58.2	39.2	88	57	1.2
HS03	23	W	57.4	38	88	55	2.4
HS04	23	M	65.1	31.1	92	63	2.1
HS07	23	W	63.5	31.4	92	61	2.5
HS15	23	W	58.3	37	88	54	4.3
HS16	24	W	59.1	35.7	89	55	4.1
HS19	24	M	54.3	42	85	52	2.3
HS21	24	W	60.9	37.4	88	55	5.9
HS17	25	M	56.6	40.3	92	66	−9.4
HS25	25	W	67	29.3	93	65	2
HS02	26	M	54.6	40.6	89	59	−4.4
HS08	26	M	62.4	38.8	89	58	4.4
HS12	26	M	58.9	43.7	87	55	3.9
HS23	26	M	52.7	36.6	84	49	3.7
HS09	27	M	57.9	40.7	84	52	5.9
HS18	27	M	62.3	31.4	92	60	2.3
HS20	27	M	54	45.4	83	51	3
HS26	28	W	52.8	38.2	85	49	3.8
HS14	31	M	52.4	40.8	87	54	−1.6
Means							2.02
SD							3.56
Older subjects							
HS13	47	W	52.5	36.8	85	48	4.5
HS29	50	W	60.1	37.6	92	64	−3.9
HS24	54	W	64.3	34.4	90	58	6.3
HS11	57	W	60.4	38	88	55	5.4
HS28	60	M	65.7	34.4	88	53	12.7
HS31	63	M	60.7	36.3	87	53	7.7
HS32	65	M	63.9	36.2	88	53	10.9
HS27	79	W	62.7	30	90	53	9.7
HS30	79	M	55.3	43.1	80	46	9.3
HS33	83	M	61.6	40.7	89	57	4.6
HS10	88	M	68.6	25.8	90	53	15.6
Means							7.53
SD							5.16

The columns show an identifier, age, sex, end-tidal P_{O_2} (PET_{O_2}), end-tidal P_{CO_2} (PET_{CO_2}), SpO_2, calculated arterial P_{O_2}, and oxygen deficit. All measurements were made when the subjects were breathing 12.5% oxygen. Note the small mean oxygen deficit of 2.02 mmHg for the young normal subjects and the higher value of 7.82 mmHg for older normal subjects. M, man; W, woman.

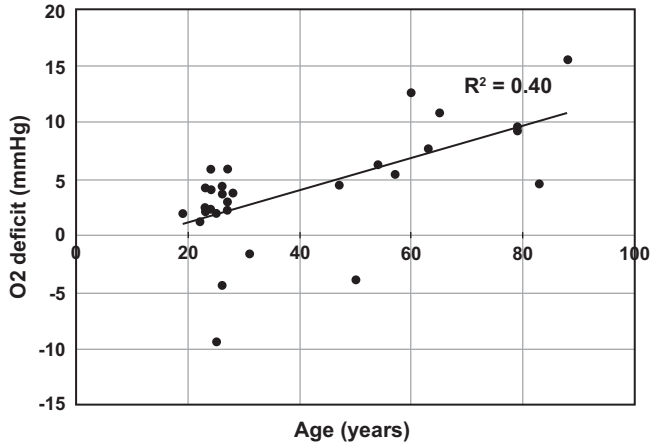

Fig. 2. Oxygen deficit plotted against age for all 31 subjects. Note that for the young normal subjects, all but two have values between about −1 and 6 mmHg. With increasing age the deficit became larger.

DISCUSSION

The most striking feature of these results is how tightly the oxygen deficit is distributed in the young normal subjects. For example, in 18 out of 20 subjects, the deficit was between about −1 and 6 mmHg with a mean value of all 20 measurements of only 2.02 mmHg. It is interesting that the SpO_2 from which these results are calculated is only accurate to within ~1–2% oxygen saturation.

It was very surprising to find that the measured O_2 deficit was so small. First, the calculation is based on the end-tidal P_{O_2}, and this depends to some extent on the volume of gas exhaled. As Fig. 1 shows, the alveolar P_{O_2} falls slightly during the expiration. Presumably, this is partly because some oxygen is being taken up by the blood during this time and that even in normal lungs poorly ventilated regions empty last. Next, all lungs have some ventilation-perfusion inequality, and this contributes to the oxygen deficit.

It may be that the calculated arterial P_{O_2} is close to the actual arterial value although this is not yet known. It is true that for many years the end-tidal P_{O_2} in normal subjects was believed to be close to the arterial P_{O_2} (1, 2). Indeed, most of the studies on the effects of P_{O_2} and P_{CO_2} on the control of ventilation have been carried out with this assumption. In any event, it is welcome news that this noninvasive technique of deriving the oxygen deficit produces such low values in young normal subjects. We know that the deficit increases substantially in lung disease (9), and therefore, this result certainly suggests that this noninvasive technique will have clinical value in assessing the impairment of a pulmonary gas exchange.

The gradual increase of the oxygen deficit with age as shown in Fig. 2 is not surprising. There are other studies on the effects of age on the traditional ideal A-a P_{O_2} difference (4, 5), and the data shown in Fig. 2 are consistent with these.

An interesting issue is the relationship between the oxygen deficit measured in normal subjects who are breathing a hypoxic mixture on the one hand and the deficit in patients who also have arterial hypoxemia but because of ventilation-perfusion inequality on the other. However it is not possible to obtain accurate information on the oxygen deficit in normal subjects without reducing their arterial oxygen saturation to less than ~94%. This ensures that we are on a steep part of the oxygen dissociation curve where the relation between P_{O_2} and saturation is tight. Calculations show that the effects of venti-

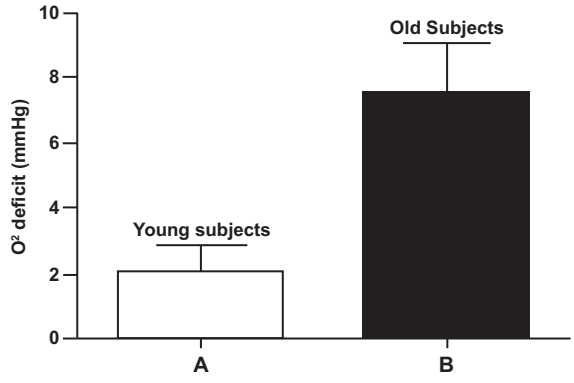

Fig. 3. Results of a nonpaired *t*-test comparing the young and old normal groups. Means ± SE are shown. Note the small mean of the young group. $P = 0.0015$.

lation-perfusion inequality on gas exchange, as measured for example by the A-a oxygen difference, are reduced as a result of alveolar hypoxia (7). Nevertheless the clear message here is that in normal subjects studied under these conditions, the oxygen deficit is extremely small and certainly very different from that in patients with lung disease.

The oxygen deficit and the traditional ideal A-a P_{O_2} difference share some similarities, but there are important differences. These have been discussed in detail elsewhere (8). Briefly, because the traditional A-a difference uses ideal alveolar gas, this index is dominated by lung units with ventilation-perfusion ratios that are less than those represented by the ideal point on the O_2-CO_2 diagram. The result is that this index mainly reflects the lung units with abnormally low ventilation-perfusion ratios. By contrast, the oxygen deficit is determined by the difference between the calculated arterial P_{O_2} and the P_{O_2} of end-tidal alveolar gas. Because the latter is closer to the composition of mixed alveolar gas than the ideal alveolar gas, the result is that the oxygen deficit better reflects the whole range of ventilation-perfusion ratios in the lung. It could be argued therefore that the oxygen deficit is a more complete description of the mechanism of impaired pulmonary gas exchange.

Some limitations of this new technique for determining impairment of pulmonary gas exchange should be noted. As emphasized above, the results are only reliable when the arterial oxygen saturation is <94% (see Ref. 6 for details). Many patients with impaired gas exchange have hypoxemia of this degree but not all. In those patients whose arterial oxygen saturation is higher, the method will not be accurate.

Some subjects showed evidence of hyperventilation as evidence by a lower than normal P_{CO_2} value, either through anxiety, or as a physiological response to the hypoxic gas mixture. This may serve to slightly elevate the O_2 deficit, but despite this values remained quite small in this normal population (Fig. 2).

Another limitation is that although we take account of the effect of changes in arterial P_{CO_2} on the oxygen affinity of hemoglobin, that is the Bohr effect, some other factors cannot be allowed for. These include alterations in base excess, body temperature, and 2,3-diphosphoglycerate concentration. The last two are not likely to be an issue for most patients. However some patients, for example, those with long-standing severe chronic obstructive pulmonary disease may have changes in base excess as a result of metabolic compensation of the respiratory acidosis. At the present time, this factor cannot be allowed for although the base excess status of a patient is now easily determined from a drop of blood from a finger prick.

In summary, this novel, noninvasive technique for measuring impaired pulmonary gas exchange gives very low values for the oxygen deficit in young normal subjects. With increasing age, the deficit increases but only by a modest amount. Since it is known that many patients with lung disease have much larger oxygen deficits (9), the conclusion is that the new method may have appreciable clinical value.

ACKNOWLEDGMENTS

We thank Dipen Makadia and Janelle Fine for assistance.

DISCLOSURES

We received support from MediPines, Corp. (Newport Beach, CA).

AUTHOR CONTRIBUTIONS

D.L.W. and G.K.P. conceived and designed research. J.B.W., D.L.W., and G.K.P. performed experiments; J.B.W., D.L.W., and G.K.P. analyzed data; J.B.W., D.L.W., and G.K.P. interpreted results of experiments; J.B.W., D.L.W., and G.K.P. prepared figures; J.B.W., D.L.W., and G.K.P. drafted manuscript; J.B.W., D.L.W., and G.K.P. edited and revised manuscript; J.B.W., D.L.W., and G.K.P. approved final version of manuscript.

REFERENCES

1. **Comroe JH, Dripps RD.** The oxygen tension of arterial blood and alveolar air in normal subjects. *Am J Physiol* 142: 700–706, 1945.
2. **Filley GF, Gregoire F, Wright GW.** Alveolar and arterial oxygen tensions and the significance of the alveolar-arterial oxygen tension difference in normal men. *J Clin Invest* 33: 517–529, 1954. doi:10.1172/JCI102922.
3. **Kelman GR.** Digital computer subroutine for the conversion of oxygen tension into saturation. *J Appl Physiol* 21: 1375–1376, 1966. doi:10.1152/jappl.1966.21.4.1375.
4. **Lilienthal JL Jr, Riley RL, Proemmel DD, Franke RE.** An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am J Physiol* 147: 199–216, 1946.
5. **Raine JM, Bishop JM.** A-a difference in O_2 tension and physiological dead space in normal man. *J Appl Physiol* 18: 284–288, 1963. doi:10.1152/jappl.1963.18.2.284.
6. **Severinghaus JW.** Simple, accurate equations for human blood O_2 dissociation computations. *J Appl Physiol Respir Environ Exerc Physiol* 46: 599–602, 1979.
7. **West JB.** Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Respir Physiol* 7: 88–110, 1969. doi:10.1016/0034-5687(69)90071-1.
8. **West JB, Prisk GK.** A new method for noninvasive measurement of pulmonary gas exchange using expired gas. *Respir Physiol Neurobiol* 247: 112–115, 2018. doi:10.1016/j.resp.2017.09.014.
9. **West JB, Crouch DR, Fine JM, Makadia D, Wang DL, Prisk GK.** A new, noninvasive method of measuring impaired pulmonary gas exchange in lung disease: an outpatient study. *Chest*. 2018 Feb 13. pii: S0012-3692(18)30253-8. [Epub ahead of print.] doi:10.1016/j.chest.2018.02.001.