Breath-by-breath assessment of alveolar gas stores and exchange

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Breath-by-breath assessment of alveolar gas stores and exchange. J Appl Physiol 96: 1464–1469, 2004. First published December 2, 2003; 10.1152/japplphysiol.01198.2003.—The volume of O₂ exchanged at the mouth during a breath (V_{O₂,m}) is equal to that taken up by pulmonary capillaries (V_{O₂,A}) only if lung O₂ stores are constant. The latter change if either end-expiratory lung volume (EELV), or alveolar O₂ fraction (F_AO₂) change. Measuring this requires breath-by-breath (BbB) measurement of absolute EELV, for which we used optoelectronic plethysmography combined with measurement of O₂ fraction at the mouth to measure V_{O₂,A} = V_{O₂,m} - (ΔEELV·F_{AO₂} + EELV·ΔF_{AO₂}), and divided by respiratory cycle time to obtain BbB O₂ consumption (V_{O₂}) in seven healthy men during incremental exercise and recovery. To synchronize O₂ and volume signals, we measured gas transit time from mouthpiece to O₂ meter and compared V_{O₂} measured during steady-state exercise by using expired gas collection with the mean BbB measurement over the same time period. In one subject, we adjusted the instrumental response time by 20-ms increments to maximize the agreement between the two V_{O₂} measurements. We then applied the same total time delay (transit time plus instrumental delay = 660 ms) to all other subjects. The comparison of pooled data from all subjects revealed r² = 0.990, percent error = 0.039 ± 1.61 SE, and slope = 1.02 ± 0.015 (SE). During recovery, increases in EELV introduced systematic errors in V_{O₂} if measured without taking ΔEELV·F_{AO₂} + EELV·ΔF_{AO₂} into account. We conclude that optoelectronic plethysmography can be used to measure BbB V_{O₂} accurately when studying BbB gas exchange in conditions when EELV changes, as during on- and off-transients.

In this paper, we take advantage of the ability of optoelectronic plethysmography (OEP) (3) to track BbB changes in end-expiratory lung volume (EELV) accurately (6) to solve this problem. When the subdivisions of lung volume are separately measured and combined with OEP and continuous measurement of gas concentrations at the mouth, it is possible to partition the uptake of O₂ and output of CO₂ at the mouth into the volumes exchanged between pulmonary capillaries and alveolar gas and changes in alveolar gas stores. Here, we present in detail the methodology we used to correct BbB V_{O₂} by use of OEP.

THEORY

Di Prampero and colleagues (4, 5) have reviewed the problems of measuring BbB V_{O₂} and we use their notation. The volume of O₂ exchanged at the mouth (V_{O₂,m}) is the difference between the volume of O₂ inspired and that expired. This is different from the amount of gas exchanged between alveolar gas and pulmonary capillaries (V_{O₂,A}) if the amount of O₂ stored in the lungs (ΔV_{O₂,s}) changes. When gas stores increase V_{O₂,m} overestimates V_{O₂,A} and vice versa when the stores decrease

\[ V_{O₂,A} = V_{O₂,m} - ΔV_{O₂,s} \]

\[ ΔV_{O₂,s} = F_{AO₂(i)}(V_{A(i)} - V_{A(i-1)}) + V_{A(i-1)} - (F_{AO₂(i)} - F_{AO₂(i-1)}) \]

where i represents the ith breath and i − 1 the immediately preceding breath. These interrelationships are illustrated with the breath shown in Fig. 1. This is a plot of O₂ fraction (F_{O₂}) at the mouth against absolute lung gas volume (V_{L}). Point B gives F_{O₂} and V_{L} at the end of breath i − 1 when the volume of O₂ remaining in the lung is given by the area ABCO, the product of OA (the end-expiratory F_{O₂}) and OC (the end-expiratory V_{L}). The inspiration of the ith breath proceeds from B to D, so the volume of O₂ inspired is given by the area BDEC.Expiration proceeds from D to G; the V_{L} expired is less than that inspired, and the F_{AO₂} at the end of breath i − 1 is less than it was at the end of breath i − 1. The expired volume of O₂ is given by the area GDEH, and the V_{O₂,m} is BDEC − GDEH, or the area BDGH. The volume of O₂ remaining in the lung at

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the end of the \( i \)th breath is given by \( \text{FGHO} \). This is less than the amount remaining at the beginning of the breath, because of a decrease in \( \text{FA}_0 \) by an amount equal to \( \text{ABKF} = V_{\text{AO}}(i-1) \) \( \text{FA}_{\text{AO}}(i) - \text{FA}_{\text{AO}}(i-1) \) but is greater than at the beginning by an amount equal to \( \text{KGHC} = \text{FA}_{\text{AO}}(i) - V_{\text{AO}}(i-1) \) because the expired volume was less than the inspired volume, thereby adding to alveolar \( O_2 \) stores. Correcting for changes in alveolar gas stores by subtracting \( \text{KGHC} \) from and adding \( \text{ABKF} \) to \( V_{\text{O}_2,\text{m}} \) reveals that the desired quantity \( V_{\text{O}_2,\text{A}} \) is given by the area \( \text{ABDG} \).

The combination of OEP with an independent measure of the subdivisions of lung volume allows accurate tracking of absolute lung volume, and, in normal subjects at least, the measurement of end-expiratory \( O_2 \) concentration is a reasonable estimate of alveolar concentration. Thus all terms on the right-hand side of Eq. 1 can be measured, allowing a direct measurement of \( V_{\text{O}_2,\text{A}} \). Dividing the measurement of \( V_{\text{O}_2,\text{A}} \) for each breath by the period for that breath gives a \( \text{BbB} \) measurement of \( V_{\text{O}_2} \).

METHODS

Subjects. We studied seven nonsmoking healthy male subjects, between 26 and 47 yr old, at rest and during an incremental exercise test. Their anthropometric characteristics and baseline lung function tests are shown in Table 1. This project was approved by the Italian Ministry of Health.

Equipment and procedures. To measure chest wall volume (\( V_{\text{cw}} \)) by OEP, 89 reflective markers were placed on the surface of the trunk ventrally and dorsally as previously described (3). The subjects were studied seated on an electrically braked cycle ergometer with their arms raised to the level of the shoulder to visualize the markers in the mid axillary line. The three-dimensional displacements of each of the reflective markers were measured by six video cameras (ELITE motion analysis system, BTS, Milano, Italy) placed in front and behind the subject and, using Gauss' theorem, \( V_{\text{cw}} \) was measured continuously (3).

The system was equipped with an accessory analog-to-digital data-acquisition system allowing recording of all other signals in parallel with OEP.

The subjects breathed with a nose clip in place, through a mouthpiece connected in series with a hot-wire anemometer flow-measuring device (Sensor Medics Vmax metabolic cart, Yorba Linda, CA), a screen-type pneumotachograph (3813 Hans Rudolph, Kansas City, MO) coupled to a pressure transducer (LCVR, 0–2 cmH\(_2\)O; Celesco Instruments, Canoga Park, CA), and a valve that separated inspired and expired flow. From time to time, mixed expired gas was collected in a Douglas bag to measure the mixed expired \( O_2 \) fraction (\( \text{Fi}_{\text{O}_2} \)). Gas was also sampled just distal to the mouthpiece to measure inspired and expired \( O_2 \) and \( CO_2 \) concentrations at the mouth with paramagnetic and infrared meters, respectively (Sensor Medics Vmax metabolic cart). The combined flow rate through both \( O_2 \) and \( CO_2 \) sampling lines was 10 ml/s. The zero-flow baseline of the pneumotachograph signal was offset in the inspiratory direction by this amount to detect zero flow at the mouth.

Before exercise was initiated, functional residual capacity (FRC) was measured by nitrogen washout (Sensor Medics Vmax metabolic cart). Each subject breathed 100% \( O_2 \) quietly while seated on the cycle ergometer until the end-tidal \( N_2 \) concentration was <1%. Lung volume change was measured by integrating the flow measured by the exercise circuit's hot-wire anemometer device. The metabolic cart calculated the volume of \( N_2 \) expired per breath from the expired \( O_2 \) and \( CO_2 \) concentrations, summed this, and, from the total amount of \( N_2 \) expired, calculated the volume of gas in the lung at the beginning of the washout period. When the washout was completed, the subject performed at least three vital capacity maneuvers that, when combined with the measurement of FRC, gave the subdivisions of lung volume.

Incremental exercise test. After FRC and the other subdivisions of lung volume were measured, the subject remained on the cycle-ergometer and breathed quietly for 5 min. Expired gas was collected in Douglas bags for the first 2 min in five subjects and for 1 min in the other two (because of technical problems with the OEP system). We then performed the exercise test starting at zero workload and increased the load in 20-W increments every 5 min up to and including 120 W. During the last 2 min (5 subjects) or 1 min (2 subjects) of each workload, expired gas was collected and mixed in a Douglas bag. \( \text{Fi}_{\text{O}_2} \) was then measured by the same \( O_2 \) meter by temporarily removing the sampling line from the mouthpiece assembly and sampling mixed expired gas from the Douglas bag.

Gold standard measurement of \( V_{\text{O}_2} \). \( V_{\text{O}_2} \) was measured by the formula \( \text{Fi}_{\text{O}_2} - \frac{V_{\text{E}}}{V_{\text{I}}}, \) where \( \text{Fi}_{\text{O}_2} \) is inspired minute ventilation, \( V_{\text{E}} \) is expired minute ventilation, and \( \text{Fi}_{\text{O}_2} \) is the inspired fraction of \( O_2 \). \( V_{\text{E}} \) and \( V_{\text{I}} \) were measured by integrating the flow as measured by the pneumotachograph to obtain inspired and expired tidal volumes, respectively, and multiplying by respiratory frequency. \( O_2 \) volume thus measured was considered as the internal gold standard of \( O_2 \) volume in conditions of stable EELV and steady-state gas-exchange conditions. This allowed avoiding any influences of differences in temperature or saturation with water between conditions because all measurements of volumes for direct comparison were performed in strictly the same manner.

Measurement of \( \text{BbB} V_{\text{O}_2} \). By measuring the difference between the amount of \( O_2 \) inspired (\( V_{\text{I}, \text{O}_2} \)) and that expired (\( V_{\text{E}, \text{O}_2} \)), we calculated \( V_{\text{O}_2,\text{m}} \) as \( V_{\text{I}, \text{O}_2} - V_{\text{E}, \text{O}_2} \). We corrected this for changes in \( O_2 \) stored within the lung during the course of the breath, as indicated in Eq. 1, calculated \( V_{\text{O}_2,\text{A}} \) for each breath, and divided by the respiratory cycle time in minutes to obtain \( V_{\text{O}_2} \). As illustrated in Fig. 1, \( V_{\text{I}, \text{O}_2} \) was calculated as the area \( \text{BDEC} \), and \( V_{\text{E}, \text{O}_2} \) was taken as the area \( \text{GDEH} \).

Table 1. Subjects' characteristics and lung volumes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Ht, cm</th>
<th>Wt, kg</th>
<th>Age, yr</th>
<th>VC, liters</th>
<th>FRC, liters</th>
<th>TLC, liters</th>
<th>RV, liters</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>178</td>
<td>70</td>
<td>33</td>
<td>5.06</td>
<td>3.71</td>
<td>7.67</td>
<td>2.61</td>
</tr>
<tr>
<td>2</td>
<td>172</td>
<td>68</td>
<td>31</td>
<td>4.81</td>
<td>3.71</td>
<td>6.51</td>
<td>1.69</td>
</tr>
<tr>
<td>3</td>
<td>165</td>
<td>78</td>
<td>26</td>
<td>3.48</td>
<td>2.67</td>
<td>4.65</td>
<td>1.18</td>
</tr>
<tr>
<td>4</td>
<td>163</td>
<td>57</td>
<td>39</td>
<td>4.14</td>
<td>4.17</td>
<td>6.45</td>
<td>2.31</td>
</tr>
<tr>
<td>5</td>
<td>170</td>
<td>56</td>
<td>20</td>
<td>4.26</td>
<td>2.36</td>
<td>5.61</td>
<td>1.34</td>
</tr>
<tr>
<td>6</td>
<td>174</td>
<td>69</td>
<td>47</td>
<td>5.29</td>
<td>3.74</td>
<td>6.82</td>
<td>1.53</td>
</tr>
<tr>
<td>7</td>
<td>166</td>
<td>60</td>
<td>34</td>
<td>4.28</td>
<td>3.52</td>
<td>5.68</td>
<td>1.40</td>
</tr>
<tr>
<td>Mean</td>
<td>170</td>
<td>65.4</td>
<td>32.9</td>
<td>4.47</td>
<td>3.41</td>
<td>6.20</td>
<td>1.72</td>
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<tr>
<td>SD</td>
<td>5.4</td>
<td>8.0</td>
<td>8.7</td>
<td>0.62</td>
<td>0.65</td>
<td>0.98</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Ht, height; Wt, weight; VC, vital capacity; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume.
To obtain this diagram, we used the volumes measured by integrating flow as measured by the pneumotachograph. We did not use OEP volumes because they included volume changes due to gas compression and any blood shifts from trunk to extremities (9). We did not use the integral of flow measured by the hot-wire anemometer system because accurate zero-flow points are difficult to detect; as zero flow is approached, the Sensorsmedics system uses a switching device to detect cooling of the hot wire by flow from the opposite direction. This obscured precise identification of zero-flow points. However, before we could use integrated pneumotachograph flow, we had to accomplish three tasks: 1) correct for integrator drift, 2) measure the time delay of the O₂-sampling line and the response time of the O₂ meter to synchronize the O₂ and volume signals precisely, and 3) correct the V_{O₂,m} for any changes in O₂ stored within the lung.

**Correction for integrator drift.** Although we did not use OEP Vcw measurements to calculate V_{O₂,m} and V_{I,O₂} because of possible errors due to gas compression and blood shifts, these errors are not present at end inspiration when alveolar pressure is atmospheric. Therefore, we measured end-inspiratory Vl as total lung capacity minus the difference between Vcw as measured at total lung capacity by OEP and end-inspiratory Vcw. For each breath, the end-inspiratory volume, measured by integrating pneumotachograph flow, was set to be equal to Vl measured by OEP, and the preceding inspiratory volume was used to measure V_{O₂,A} and the following expiration to calculate V_{O₂,A} for that particular breath. Each BbB V_{O₂} measurement was treated as a separate discrete event.

**Avoiding temperature effects on gas volumes.** To avoid any influences of differences in temperature between conditions, all measurements of volumes for direct comparison were performed in strictly the same manner, i.e., with the pneumotachograph.

**Synchronization of O₂ and Vl signals.** To synchronize the O₂ and Vl signals, we had to measure the delay time for a quantum of gas to travel the length of the sampling tube from the mouthpiece assembly to the paramagnetic O₂ meter and the response time of the meter. To do this, we made a circuit similar in principle to the one reported by Proctor and Beck (11), consisting of a chamber covered by a rubber membrane covered with a piece of aluminum foil. The chamber contained a mixed expired gas sample. The gas-sampling line was removed from the exercise circuit, and an 18-gauge needle was attached to the inlet port. The needle was connected to a battery, the other pole of which was connected to the aluminum foil and the analog-to-digital board. Thus, when the needle was plunged rapidly through the foil, from air to mixed expired gas, it completed the electrical circuit, generating a signal the instant that the gas being sampled changed. From this we measured the delay time as the time between the generation of the electrical signal and the instant the O₂ concentration began to fall. An example of the tracings obtained is shown in Fig. 2. As can be seen in this figure, the response of the meter was sigmoid shaped, which represents a combination of diffusive mixing at the front between mixed expired gas and fresh air, plus the instrumental response time. We were unable to measure the meter’s response time accurately for two reasons: 1) the sigmoid response was not symmetrical; the initial fall in O₂ concentration was sharper than the curve at the final plateau, and thus we could not precisely distinguish between diffusive mixing and the instrumental response time; 2) the sampling rate of the OEP system was 50 Hz so the resolution of the common time base was 20 ms. Because the instrumental response time was on the order of 100 ms, our time-base resolution did not permit a precise measurement of the response time.

To deal with this problem, we compared the gold standard measurement of V_{O₂} with one subject’s values of the mean BbB V_{O₂} measured at each workload over the same time period. This gave us a plot of all measured values to the gold standard at 660 ms. At 680 ms, five individuals had an intercept closer to zero at 640 ms, their values for slope showed better agreement with the gold standard at 660 ms. At 680 ms, five individuals had an intercept closer to zero than at 660 ms, but in four of these the values of slope, r², and percent error were as good as or better at 660 ms. Only one individual had better values for intercept, slope, and r² at 680 ms, but the percent error at that time delay was 8.9% compared with 3.8% at 660 ms. We concluded that in our setup a total time delay of 660 ms provides the most accurate measurement of BbB V_{O₂}. This conclusion is also supported by

![Fig. 2. Diagram illustrating how the time delay of the O₂ sampling and response time of the O₂ meter were measured. A needle was fitted to the end of the sampling catheter and thrust through a patch of aluminum foil into a bag containing mixed expired gas. This closed an electrical circuit shown by the vertical deflection of the lower line, at time 1. The O₂ concentration as shown in the upper line began to fall at time 2. Time 2 − 1 gives the transit time for a quantum of gas to travel from the port of the sampling tube at the mouthpiece to the meter. Because the sampling rate of the optoelectronic plethysmograph (OEP) system was 50 Hz, we tried various points at 20-ms increments along the downward slope of the O₂ curve, for total time delays of 620–700 ms, to determine which time delay gave values of breath-by-breath (BbB) O₂ uptake (V_{O₂}) closest to the gold standard.](http://jap.physiology.org/ http://jap.physiology.org/)

**RESULTS**

Table 2 gives the values of slope, intercept, r², and percent error of the linear regressions between the gold standard measurement of V_{O₂} and mean BbB V_{O₂} in each individual at each of the four time delays. A total time delay of 660 ms gave the best fit to the gold standard measurement V_{O₂}. Although two individuals had an intercept closer to zero at 640 ms, their values for slope showed better agreement with the gold standard at 660 ms. At 680 ms, five individuals had an intercept closer to zero than at 660 ms, but in four of these the values of slope, r², and percent error were as good as or better at 660 ms. Only one individual had better values for intercept, slope, and r² at 680 ms, but the percent error at that time delay was 8.9% compared with 3.8% at 660 ms. We concluded that in our setup a total time delay of 660 ms provides the most accurate measurement of BbB V_{O₂}. This conclusion is also supported by
the mean values, which were better in every category at a time delay of 660 ms than at the other three delays. When this value was used, the percent error ranged from $3.6$ to $7.0\%$, but the mean value was only $2.4\%$.

Figure 3A is a pooled comparison in all subjects between the mean BbB $\dot{V}O_2$ and the gold standard $\dot{V}O_2$, using the different time delays. The lines are the linear regressions for each time delay. Each datum is a single point from one subject at a given exercise level. Thus, for any given time delay, the regression line for 660 ms is closest to the identity line.

Bland-Altman analysis of the similarity between BbB and gold standard measures of $\dot{V}O_2$ ($\dot{V}O_2,ss$) at delay times of 620 (A), 640 (B), 660 (C), 680 (D), and 700 (E) ms. Solid horizontal line, mean of the data; dashed lines, $\pm 2$ SD. At a delay of 660 ms, error and trend are smallest.

Table 2. Comparison of gold standard and BbB measurement of $\dot{V}O_2$: individual slope, $r^2$, and errors at different delay times

<table>
<thead>
<tr>
<th>Delay</th>
<th>620 ms</th>
<th>640 ms</th>
<th>660 ms</th>
<th>680 ms</th>
<th>700 ms</th>
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<tr>
<td></td>
<td>Int. Slope</td>
<td>$r^2$</td>
<td>err%</td>
<td>Int. Slope</td>
<td>$r^2$</td>
</tr>
<tr>
<td>1</td>
<td>0.02 0.915 0.993 -5.5 0.04 0.955 0.994 0.6 0.06 0.988 0.994 7.0 0.07 1.027 0.993 13.5 0.09 1.050 0.993 18.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.06 0.982 0.996 -11.4 -0.04 1.019 0.997 -4.4 -0.02 1.057 0.997 2.6 -0.01 1.093 0.997 9.6 0.01 1.127 0.997 16.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.09 0.839 0.999 -6.7 0.07 0.907 0.999 -1.6 0.05 0.974 0.998 3.2 0.04 1.037 0.997 8.0 0.02 1.099 0.997 12.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-0.09 0.984 0.998 -21.0 -0.07 1.038 0.999 -12.2 -0.06 1.094 0.999 -3.6 -0.05 1.146 0.999 4.7 -0.04 1.196 0.998 13.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.07 0.897 0.994 -2.1 0.07 0.934 0.995 1.5 0.07 0.972 0.996 5.1 0.06 1.010 0.997 8.4 0.06 1.046 0.997 11.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>0.09 0.876 0.996 -4.8 0.08 0.924 0.998 -0.6 0.07 0.965 0.998 3.8 0.08 1.005 0.999 8.9 0.07 1.047 0.999 13.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.02 0.846 0.989 -13.6 -0.00 0.929 0.992 -7.3 -0.03 1.019 0.992 -1.4 -0.05 1.097 0.991 4.6 -0.07 1.181 0.990 10.2</td>
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Mean

<table>
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<tr>
<th>Slope</th>
<th>$r^2$</th>
<th>err%</th>
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<tbody>
<tr>
<td>Int.</td>
<td>0.02 0.906 0.995 -9.3 0.02 0.958 0.996 -3.4 0.02 1.010 0.996 2.4 0.02 1.059 0.996 8.3 0.02 1.106 0.996 13.7</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>0.03 0.022 0.001 2.5 0.02 0.019 0.001 1.9 0.02 0.019 0.001 1.4 0.02 0.020 0.001 1.1 0.02 0.024 0.001 1.1</td>
<td></td>
</tr>
</tbody>
</table>

Int., intercept; err%, percent error. BbB, breath by breath.

Fig. 3. A: identity plot of BbB $\dot{V}O_2$ against the steady-state (SS; gold standard) method at different transit times plus instrumental response delays. Each line is the linear regression for pooled data in all subjects at every exercise level. Each datum therefore is the result in 1 individual at a given exercise workload.

Fig. 4. Bland-Altman analysis of the similarity between BbB and gold standard measures of $\dot{V}O_2$ ($\dot{V}O_2,ss$) at delay times of 620 (A), 640 (B), 660 (C), 680 (D), and 700 (E) ms. Solid horizontal line, mean of the data; dashed lines, $\pm 2$ SD. At a delay of 660 ms, error and trend are smallest.
consists of the \( \dot{V}O_2 \) values measured at each exercise workload in each subject. This figure also shows that at a delay time of 660 ms the BbB measurement of \( \dot{V}O_2 \) is closest to the gold standard.

This is shown even more clearly in Fig. 3, B and C. Figure 3B plots the slope \( \pm SE \) of the regression, and Fig. 3C the \( r^2 \) value against the time delay. A delay time of 660 ms gives a slope close to 1 and the highest \( r^2 \) value.

Figure 4 shows the Bland-Altman analysis comparing the difference between the BbB estimate of \( \dot{V}O_2 \) and the steady-state \( \dot{V}O_2 \) measurements for the different time delays. Again the time delay of 660 ms gives the optimal result. At a time delay of 660 ms, the average percent error was negligible.

When changes in lung \( O_2 \) stores are random because of random fluctuations in EELV, the average \( \dot{V}O_2 \) will be close to \( \dot{V}O_2,A \), because the errors due to increases in EELV will be cancelled by errors due to the decreases. However, when EELV changes systematically, such as during the onset and end of exercise or during dynamic hyperinflation, the error will be systematic. This is illustrated in Fig. 5. Figure 5A shows the systematic increase in EELV at the end of exercise (marked by the left-hand arrow). Between the two arrows, EELV increases by more than 0.5 liter. Figure 5B shows the \( F_O_2 \) vs. absolute lung volume loops moving BbB to the right during this recovery period. Figure 5C is an identity plot of the \( \dot{V}O_2 \) at the mouth (ordinate) vs. the \( \dot{V}O_2 \) by the pulmonary capillaries as measured by OEP on the abscissa. All but two points lie above the line of identity. Figure 5D is a Bland-Altman analysis demonstrating the systematic nature of the error. Figure 5E shows \( \dot{V}O_2,A \) and \( \dot{V}O_2,m \) as a function of time after the end of exercise.

**DISCUSSION**

The main finding reported here is that it is now technically feasible to correct BbB measurements of \( \dot{V}O_2 \) measured at the mouth for changes in pulmonary \( O_2 \) content. To date, the unknown changes in EELV made this correction difficult. In addition to the error introduced by changes in EELV, the correction for differences in gas concentration at the beginning and end of the breath requires a BbB measurement of absolute gas volume. The absence of a solution to this problem has been the principal reason that accurate measures of BbB gas exchange have not generally been available. Even in a whole body plethysmograph, thermal

![Fig. 5. Diagrams illustrating the systematic error in BbB \( \dot{V}O_2 \) measurement when there is a systematic change in end-expiratory lung volume (EELV). A: OEP tracings of total chest wall volume (Vcw) change at the end of exercise and during recovery after. The end of exercise is at 38 s (left arrow), and with time EELV then changes. To emphasize the effect of EELV, a series of breaths when changes in EELV are particularly big (between the 2 arrows) are shown in B, C, and D. B: \( F_O_2 \) vs. \( V_L \) plots during recovery from exercise between the 2 arrows shown in A. The progressive increase in EELV displaced the loops progressively to the right, increasing the \( O_2 \) stored within the lung. When this is not taken into account, the \( F_O_2 \)-vs.-\( V_L \) diagram is not a closed loop because the EELV is greater at the end of the breath than at the beginning. This leads to an overestimate of BbB \( \dot{V}O_2 \) as shown in C, which is an identity plot of \( \dot{V}O_2 \) by the pulmonary capillaries (\( \dot{V}O_2,A \)) vs. \( \dot{V}O_2,m \) calculated by measuring the difference between the volume of \( O_2 \) inspired minus the volume expired. D: Bland-Altman analysis of the data shown in C. E: BbB \( \dot{V}O_2 \) (A) and \( \dot{V}O_2,m \) (C) as a function of time. \( \dot{V}O_2,m \) overestimates \( \dot{V}O_2 \) by the pulmonary capillaries in the first period because of the changes in pulmonary \( O_2 \) stores. Exponential curves fitting the 2 data sets are also shown. The time constant \( t \) of the \( \dot{V}O_2,m \) off-transient was 46.1 s and that of the \( \dot{V}O_2,A \) 43.1 s.](http://jap.physiology.org/10.220.33.5/copied_for_upload/Fig_5.png)
instability and humidity changes make continuous tracking of absolute volume difficult, and measurements during exercise have been hitherto impossible. This led Gronlund (8) to take a different approach to calculate \( \bar{V}_O_2 \) by choosing points on the expiratory tracings where \( F_O_2 \) were identical so that \( V_L \cdot \Delta F \) became zero. OEP offers another solution to this problem because it can track absolute lung volume on a continuous basis.

This is particularly useful when on- and off-transients of exercise are studied, when the changes in \( V_O_2 \) measured at the mouth are often used to study transients in \( V_O_2 \) at tissue level. For illustration of this fact, we collected data during the off-transient at the end of an exercise bout in one subject. EELV changed over time during the off-transient of exercise (Fig. 5A), and these changes were accompanied by changes in end-expiratory \( O_2 \) fractions (Fig. 5B). Together, this led to an overestimation of \( O_2 \) uptake due to an increase in \( O_2 \) stores in the lung as shown on a BbB basis in Fig. 5, C and D.

In Fig. 5E, the effect on the time constant of BbB changes in \( V_O_2 \) during the off-transient is shown. The data were fitted with the following exponential function: \( y = y_0 + \alpha \times \exp(-t/\tau) \). With correction for changes in lung \( O_2 \) stores, \( \tau \) was 43.1 s, whereas in the uncorrected condition it was 46.1 s, a difference of 6.5%. Furthermore, the uncorrected data are poorly fitted by a single exponential.

In a recent paper, Capelli and colleagues (4) reviewed the problems of using conventional BbB measurement of gas exchange at the mouth. They reviewed and compared different techniques to take into account the errors induced in situations in which alveolar gas stores do not remain constant between successive breaths. Capelli et al. concluded that the method of Gronlund (8) based on the definition of a breath being the period between two identical values of gas concentrations at the mouth was a promising way to improve the accurateness of BbB gas exchange at the mouth. In a subsequent paper (5), Capelli and colleagues showed that this method allows BbB measurement of alveolar gas exchange during on-transients of exercise. However, all the known methods require certain a priori assumptions to be made, of which the precise effect on the error of measurement remains obscure. Our method, which essentially represents a solution to the original idea by Linnarson (10), does not require any assumption about initial alveolar stores or the assumption that expired gas concentrations at the mouth faithfully reflect alveolar gas concentrations.

In conclusion, OEP allows the measurement of BbB \( V_O_2 \) at the alveolar-capillary interface during non-steady-state conditions such as the on- or off-transients of exercise, fully taking into account BbB changes in EELV and lung \( O_2 \) stores. It thus becomes a method of choice for the study of the relationship between \( O_2 \) uptake in the blood in the lung and peripheral \( O_2 \) consumption.

**REFERENCES**


