An Assessment of Overall “Gain” of the O₂-feedback Control System with and without External Dead Space Breathing

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Abstract Overall gain of the O₂-ventilation feedback control system ($G_{O_2}$) was determined in 9 male and one female healthy subjects. $G_{O_2}$ progressively increased with decreasing end-tidal $P_{O_2}$ ($P_{ET_{O_2}}$). This value did not exceed the overall gain of the CO₂-ventilation feedback system ($G_{CO_2}$) even at a $P_{ET_{O_2}}$ level of 40 mmHg, suggesting that hypoxic stimulation did not become predominant in the present experimental condition.

With addition of 250 ml of external dead space, $P_{ET_{O_2}}$ decrement ($\Delta P_{ET_{O_2}}$·actual) was experimentally observed. The $\Delta P_{ET_{O_2}}$·actual thus obtained was found to be in good agreement with the $P_{ET_{O_2}}$ decrement deduced from $G_{O_2}$ ($\Delta P_{ET_{O_2}}$·expected). This result was similar to that found in the $P_{ET_{CO_2}}$ change previously seen in normoxia.

Key Words: overall gain, ventilatory control, dead space, hypoxia, peripheral chemoreceptors.

The concept of overall “gain” of the CO₂-feedback control system ($G_{CO_2}$) was first proposed by Severinghaus (1972), and briefly quoted by Berger et al. (1977). This corresponds to the negative value of the open-loop gain advocated by Milhorn (1966). This gain might be defined as the unitless product of the two transfer functions in the CO₂ negative feedback loop. The overall gain under normoxic conditions was fully investigated by Honda et al. (1981, 1983). Also, controller gain during hypoxia and hypercapnia was investigated by Swanson et al. (1978), Bellville et al. (1979), and Cherniack et al. (1979).

In the present study our interest is directed toward the overall “gain” of the O₂-ventilation feedback control system ($G_{O_2}$). We referred to the concept of the gain designated by Berger et al. (1977) and defined $G_{O_2}$ as the ratio of the two values, i.e., the slope of the hypoxia response curve ($S'$) versus that of the metabolic hyperbola ($SL'$). When a disturbance is introduced into the system so as to shift $P_{ET_{O_2}}$ by $\Delta P_{ET_{O_2}}$, the final deviation in $P_{ET_{O_2}}$, will be $\Delta P_{ET_{O_2}}/(1-G_{O_2})$. In experiments with external dead space breathing, the validity of such a prediction
by using the $G_0$, was assessed by comparing the predicted values with actual 
$P_{ET_0}$, changes experimentally produced. We also compared $G_0$ with $G_{CO_2}$.

**MATERIALS AND METHODS**

**Subjects.** The experiments were performed on a healthy group of 9 males 
and one female from 22 to 56 years of age. Table 1 shows the physical charac-
teristics of the subjects. The subjects were briefly informed of the experimental 
procedures but not the purpose or results of any of the experiments (except sub-
jects Y.H. and H.M.) until the study had been completed.

**Experimental setup.** The experimental setup used in this study is schematical-
ly shown in Fig. 1. The external dead space (DS) used was a plastic tube of 250 
ml capacity (12.5 cm in length and 5 cm in internal diameter). Volume of the 
expired air was measured by a wet gasometer and the concentrations of $O_2$ and 
$CO_2$ were analyzed by a respiratory mass-spectrometer (Hitachi 503 respiratory 
gas analyzer). The amount of air in the closed circuit was about 18 liters. A 9-
liter spirometer (Benedict-Roth type) and a plastic reservoir box, which was about 
3 liters in capacity, were incorporated into the circuit. The total respiratory 
resistance in the closed circuit at a flow rate of 1.0 liter·sec$^{-1}$ was 1.0 cmH$_2$O· 
liter$^{-1}$·sec$^{-1}$. When the DS was added to the line, the resistance was 1.7 cmH$_2$O· 
liter$^{-1}$·sec$^{-1}$. A sampling tube to the respiratory mass-spectrometer was inserted 
into a mouthpiece in order to have its tip situated near the mouth. Breath-by-
breath end-tidal $P_{CO_2}$ and $P_{O_2}$ ($P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$) were simultaneously recorded. 
The electric signal from a potentiometer attached to a pulley of the spirometer was 
fed into an amplifier, which provided breath-by-breath minute volume as well as 
tidal volume. The former was recorded by a digital printer when desired. The 
respiratory rate was calculated from the original recordings as shown in Fig. 2.

Table 1. Physical characteristics of the subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Body height (cm)</th>
<th>Body weight (kg)</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y.H.</td>
<td>56</td>
<td>163.0</td>
<td>72.0</td>
<td>Male</td>
</tr>
<tr>
<td>Y.S.</td>
<td>36</td>
<td>168.0</td>
<td>63.0</td>
<td>Male</td>
</tr>
<tr>
<td>F.H.</td>
<td>31</td>
<td>174.0</td>
<td>79.0</td>
<td>Male</td>
</tr>
<tr>
<td>Y.M.</td>
<td>30</td>
<td>165.0</td>
<td>71.0</td>
<td>Male</td>
</tr>
<tr>
<td>H.M.</td>
<td>28</td>
<td>167.0</td>
<td>60.0</td>
<td>Male</td>
</tr>
<tr>
<td>A.Y.</td>
<td>33</td>
<td>168.0</td>
<td>64.0</td>
<td>Male</td>
</tr>
<tr>
<td>Y.N.</td>
<td>37</td>
<td>172.0</td>
<td>71.0</td>
<td>Male</td>
</tr>
<tr>
<td>H.K.</td>
<td>30</td>
<td>172.0</td>
<td>72.0</td>
<td>Male</td>
</tr>
<tr>
<td>N.A.</td>
<td>22</td>
<td>154.3</td>
<td>41.0</td>
<td>Female</td>
</tr>
<tr>
<td>Y.O.</td>
<td>35</td>
<td>170.0</td>
<td>75.0</td>
<td>Male</td>
</tr>
<tr>
<td>Mean</td>
<td>33.8</td>
<td>167.1</td>
<td>66.8</td>
<td></td>
</tr>
<tr>
<td>±S.D.</td>
<td>± 9.0</td>
<td>± 5.7</td>
<td>± 10.1</td>
<td></td>
</tr>
</tbody>
</table>

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OVERALL GAIN OF $O_2$-FEEDBACK SYSTEM

Experimental procedures. The subjects were seated on a comfortable dental chair in a semi-recumbent position. They were tested 2 hr or more after breakfast. In the DS run, they breathed through the mouthpiece and a respiratory valve between which the plastic tube used for the DS had been inserted. At least 10 min after the start of the experimental run, expired air was collected for 5 min into a Douglas bag during which time the steady state condition was confirmed to be maintained. After this, they breathed in the closed circuit only, and were subjected to a progressive hypoxia test similar to the method of Weil et al. (1970). The expired air was sampled from the plastic reservoir box at PETO$_2$, levels of 80, 60, 50, 45, and 40 mmHg, respectively. With increasing ventilation due to pro-
gressive hypoxia, $P_{ETCO_2}$ tended to decrease. Therefore, $P_{ETCO_2}$ was maintained constant by adjusting the rate of bypass flow to a CO$_2$ absorber placed in the spirometer.

One hour or more after the DS run, another progressive hypoxia test, the control run, was carried out while maintaining $P_{ETCO_2}$ at the same level with the first run without using DS. The equivalent levels of inspired $P_{O_2}$, which had been found to attain $P_{ETO_2}$ of 80, 60, 50, 45, and 40 mmHg in the DS run, were first ascertained in this control run. The $P_{ETO_2}$ corresponding to each of these inspired $P_{O_2}$ levels were determined ($P_{ETO_2}$·control). The differences between the $P_{ETO_2}$·
control and the corresponding values for $P_{ET_{O_2}}$ in the DS run were considered to be experimentally induced $P_{ET_{O_2}}$ change due to DS loading and defined as $\Delta P_{ET_{O_2}}$ actual. Expired air was also obtained and analyzed at these particular $P_{ET_{O_2}}$ levels.

Data analysis and calculation of expected $P_{ET_{O_2}}$ change from the $G_{O_2}$. From the $P_{ET_{O_2}}$ control and the corresponding expired minute volumes ($\dot{V}E$) obtained from the control run, the ventilatory response to hypoxia was calculated. It was evaluated using a modified hyperbola equation (Weil et al., 1970) originally advocated by Lloyd and Cunningham (1963).

$$\dot{V}E = \dot{V}O + \frac{A}{(P_{ET_{O_2}} - C)},$$

where $\dot{V}E$ is the minute volume, $\dot{V}O$ the horizontal asymptote in ventilation for infinite $P_{ET_{O_2}}$, $A$ the slope constant of the hyperbola expressing the degree of hypoxic sensitivity of the subject, and $C$ the vertical asymptote in $P_{ET_{O_2}}$ for infinite $\dot{V}E$. To obtain the above three parameters in the equation, $C$ was first determined by a curve-fitting procedure using a microcomputer (Apple II), i.e., the $C$ value which gave the best correlation coefficient between $\dot{V}E$ and $1/(P_{ET_{O_2}} - C)$. Then, from the linear regression between $\dot{V}E$ and $1/(P_{ET_{O_2}} - C)$, $\dot{V}O$ and

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Schematic illustration of the $O_2$-ventilation feedback system and of predicted changes due to external dead space. $\Delta \dot{V}_D$-effective: increment of effective dead space ventilation.}
\end{figure}
A were determined as the intercept at the ordinate and the slope of the regression line, respectively.

Figure 3 illustrates the O₂-ventilation feedback system and the expected changes when the external dead space is applied to the system. At the control condition, $\overline{P_{ET}}_0$, is settled at point X which is the intercept of the hypoxia response curve and the metabolic hyperbola (CUNNINGHAM, 1974). The slope of the former is defined as $S'$ and the latter as $S''$. The gain ($G_{O_2}$) of the control system is defined as $S'/S''$ which is the negative value due to the negative feedback system. Now, the addition of $\Delta V_D \cdot$ effective reduces $\dot{V}_A$ by the amount indicated as XY, and thus $\overline{P_{ET}}_0$, will decrease by YZ. However, at the same time the $\overline{P_{ET}}_0$, decrease stimulates ventilation and $\overline{P_{ET}}_0$, increases along the line of metabolic hyperbola. A new equilibrium condition will be settled at point U, which is the intercept of the new hypoxia response curve (broken line) and the metabolic hyperbola. The ratio YZ/YV indicates the capacity of the overall O₂-ventilation feedback system, and can be expressed as $(1 - G_{O_2})$ or $(1 + |G_{O_2}|)$ as shown in the figure.

According to the above considerations, the magnitude of YV which is defined $\Delta \overline{P_{ET}}_0$, expected can be calculated as follows:

$$\Delta \overline{P_{ET}}_0$, expected = YV = \frac{YZ}{1 - G_{O_2}} = \frac{\Delta \dot{V}_D \cdot \text{effective}}{S'} \cdot \frac{1}{1 - G_{O_2}} = \frac{\Delta \dot{V}_D \cdot \text{effective}}{S'(1 - G_{O_2})}.$$  

Metabolic hyperbola shifts in parallel on the abscissa when inspired O₂ level changes. The slope of metabolic hyperbola to altered $\dot{V}_A$ does not change with this parallel shift. Therefore,

$$\frac{d \overline{P_{ET}}_0}{d \dot{V}_A} = \frac{d(P_{ET} - P_{I_0})}{d \dot{V}_A}.$$  

From the volume as well as O₂ and CO₂ concentrations of the expired air collected in a Douglas bag, the O₂ production was calculated. Then, the slope of the metabolic hyperbola to the $\overline{P_{ET}}_0$, axis in the DS run was calculated as follows:

From (1)

$$\frac{d \dot{V}_A}{d \overline{P_{ET}}_0} = \frac{d \dot{V}_A}{d(P_{ET} - P_{I_0})},$$

when the difference between inspiratory ($\dot{V}_i$) and expiratory minute volume ($\dot{V}_e$) is neglected,

$$\dot{V}_A = 0.863 \times \frac{\dot{V}_{o_2}}{P_{I_0} - \overline{P_{ET}}_0} = -0.863 \times \frac{\dot{V}_{o_2}}{P_{ET} - P_{I_0}},$$  

so,

$$\frac{d \dot{V}_A}{d(P_{ET} - P_{I_0})} = 0.863 \times \frac{\dot{V}_{o_2}}{(P_{ET} - P_{I_0})^2}.$$
Therefore,
\[ SL' = 0.863 \times \frac{\dot{V}_o}{(P_{ET_{O_2}} - P_{I_{O_2}})^2} . \]  

From the equation \[ \dot{V}_E = \dot{V}_o + A/(P_{ET_{O_2}} - C), \]
\[ d\dot{V}_E/dP_{ET_{O_2}} = -A/(P_{ET_{O_2}} - C)^2. \]  

As \[ \dot{V}_E = \dot{V}_A + \dot{V}_D \] where \[ \dot{V}_D \] is estimated to be a constant value,
\[ \frac{d\dot{V}_E}{dP_{ET_{O_2}}} = \frac{d\dot{V}_A}{dP_{ET_{O_2}}}. \]  

From Eqs. (4) and (5),
\[ S' = \frac{d\dot{V}_A}{dP_{ET_{O_2}}} = -A/(P_{ET_{O_2}} - C)^2. \]  

Because \( G_{O_2} \) is equal to \( S'/SL' \), this can be obtained from the product of Eq. (6) and the reciprocal of Eq. (3).

Effective dead space ventilation in each experimental run was calculated from \( \dot{V}_E, P_{ET_{CO_2}} \), expired \( (P_{E_{CO_2}}) \) and inspired \( P_{CO_2} \) \( (P_{I_{CO_2}}) \) using the Bohr equation. The increment of the effective dead space ventilation from the control to the DS run was defined as \( \Delta \dot{V}_D \cdot \text{effective} \).

\[ \Delta \dot{V}_D \cdot \text{effective} = \frac{P_{ET_{CO_2}} - P_{E_{CO_2}}}{P_{ET_{CO_2}} - P_{I_{CO_2}}} \times \dot{V}_E(\text{DS}) - \frac{P_{ET_{CO_2}} - P_{E_{CO_2}}}{P_{ET_{CO_2}} - P_{I_{CO_2}}} \times \dot{V}_E(\text{C}), \]

where \( \dot{V}_E(\text{DS}) \) and \( \dot{V}_E(\text{C}) \) represent \( \dot{V}_E \) in the DS and the control run, respectively.

The decrement in \( P_{ET_{O_2}} \), deduced from \( G_{O_2} \) \( (\text{defined } P_{ET_{O_2}} \cdot \text{expected}) \) was calculated as follows:

\[ \Delta P_{ET_{O_2}} \cdot \text{expected} = \Delta \dot{V}_D \cdot \text{effective}/(SL' \times (1 - G_{O_2})). \]

This value was compared with \( \Delta P_{ET_{O_2}} \cdot \text{actual} \) which was the actual decrement in \( P_{ET_{O_2}} \) due to the addition of the external dead space described in the former section.

RESULTS

Figure 2 illustrates an example of progressive hypoxia response of the subject Y.H. in the DS and control run.

The mean values and standard deviations of \( G_{O_2} \) in the control run, at \( P_{ET_{O_2}}, \)
80, 60, 50, 45, and 40 mmHg, were \(-0.16 \pm 0.19, -0.16 \pm 0.15, -0.17 \pm 0.13, -0.38 \pm 0.22, \) and \(-4.70 \pm 11.8, \) respectively. Those of \( G_{O_2} \) in the DS run, at \( P_{ET_{O_2}} \) 80, 60, 50, 45, and 40 mmHg, were \(-0.52 \pm 0.60, -0.64 \pm 0.34, -0.67 \pm 0.36, -0.84 \pm 0.58, \) and \(-4.46 \pm 8.76, \) respectively (Table 2). No significant difference between the mean values of \( G_{O_2} \) in DS and control run was detected. In this table, the data of subj. H.K. was excluded because the difference in ventilatory response
Table 2. Results obtained from progressive hypoxia test with and without external dead space.

<table>
<thead>
<tr>
<th>( P_{ETO_2} ) (mmHg)</th>
<th>80</th>
<th>60</th>
<th>50</th>
<th>45</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall gain (( G_{O_2} ))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>-0.52±0.60</td>
<td>-0.64±0.34</td>
<td>-0.67±0.36</td>
<td>-0.84±0.58</td>
<td>-4.46±8.76</td>
</tr>
<tr>
<td>(-)</td>
<td>-0.16±0.19</td>
<td>-0.16±0.15</td>
<td>-0.17±0.13</td>
<td>-0.38±0.22</td>
<td>-4.70±11.8</td>
</tr>
<tr>
<td>Metabolic hyperbola ( \frac{d\dot{V}<em>A}{dP</em>{ETO_2}}(SL') ) (liters·min(^{-1}·mmHg(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>0.22±0.09</td>
<td>0.39±0.18</td>
<td>1.00±0.72</td>
<td>2.08±2.41</td>
<td>2.87±2.32</td>
</tr>
<tr>
<td>(-)</td>
<td>0.43±0.24</td>
<td>0.86±0.54</td>
<td>1.84±1.22</td>
<td>2.33±2.21</td>
<td>5.48±6.46</td>
</tr>
<tr>
<td>Hypoxia response curve ( \frac{d\dot{V}<em>A}{dP</em>{ETO_2}}(S') ) (liters·min(^{-1}·mmHg(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>-0.11±0.13</td>
<td>-0.28±0.23</td>
<td>-0.59±0.38</td>
<td>-1.08±0.62</td>
<td>-4.04±2.83</td>
</tr>
<tr>
<td>(-)</td>
<td>-0.06±0.08</td>
<td>-0.14±0.17</td>
<td>-0.31±0.32</td>
<td>-0.78±0.59</td>
<td>-6.24±8.97</td>
</tr>
<tr>
<td>( \Delta \dot{V}_D \cdot \text{effective} ) (liters·min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.39±1.15</td>
<td>4.53±1.60</td>
<td>5.90±2.50</td>
<td>6.82±4.24</td>
<td>9.50±8.36</td>
</tr>
<tr>
<td>Minute volume ( \dot{V}_T ) (liters·min(^{-1})) (BTPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>12.7±2.8</td>
<td>15.3±4.1</td>
<td>19.7±7.9</td>
<td>24.3±11.2*</td>
<td>33.2±12.8*</td>
</tr>
<tr>
<td>(-)</td>
<td>12.6±4.0</td>
<td>15.3±4.8</td>
<td>18.3±7.8</td>
<td>21.1±10.7</td>
<td>28.3±12.6</td>
</tr>
<tr>
<td>Tidal volume ( V_T ) (ml) (BTPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>800±180</td>
<td>900±150</td>
<td>1,080±290</td>
<td>1,290±350*</td>
<td>1,750±300*</td>
</tr>
<tr>
<td>(-)</td>
<td>750±160</td>
<td>850±140</td>
<td>1,000±260</td>
<td>1,150±350</td>
<td>1,430±290</td>
</tr>
<tr>
<td>Respiratory rate ( f ) (breath·min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>16.6±5.3</td>
<td>17.2±4.7</td>
<td>18.2±5.1</td>
<td>18.3±5.4</td>
<td>18.7±5.7</td>
</tr>
<tr>
<td>(-)</td>
<td>17.3±5.5</td>
<td>18.3±6.1</td>
<td>18.6±6.4</td>
<td>18.4±6.6</td>
<td>19.8±7.4</td>
</tr>
</tbody>
</table>

DS run: the test conducted with 250 ml external dead space.
Control run: the test conducted without external dead space.
Each value represents the mean ± standard deviation. [**][**] indicate that significant increment in \( G_{O_2} \) is seen from consecutive high to low \( P_{ETO_2} \) levels (\( p<0.05 \), (\( p<0.01 \), respectively (paired t-test). * shows that the difference from the data of the control run to those of the DS run is significant (\( p<0.05 \)). (+) implies the data of the DS run. (-) implies the data of the control run. All values were calculated from the data of 9 subjects in the resting condition. Because the difference in ventilatory response between control and DS run of subject H.K. at \( P_{ETO_2} \) 40 mmHg was exceedingly large, the data of subject H.K. could be excluded with the Smirnov's analysis.
between DS and control run was so large, particularly at $P_{ETO_2}$ 40 mmHg, that his data could be excluded according to Smirnov's analysis. A significant increment in $G_o$, in the control run was seen from 50 to 45 mmHg $P_{ETO_2}$ level. $\Delta V'_D$, effective, and $S'_L$ and $S''_L$ in both DS and control runs increased as $P_{ETO_2}$ decreased.

The mean values and standard deviations of $V_O$, $A$, and $C$ in the DS run were $5.70 \pm 7.83$ (liters $\cdot$ min$^{-1}$), $407 \pm 646$ (liters $\cdot$ min$^{-1}$ $\cdot$ mmHg), and $29.1 \pm 10.1$ (mmHg), respectively. Those in the control run were $9.03 \pm 7.02$ (liters $\cdot$ min$^{-1}$), $280 \pm 443$ (liters $\cdot$ min$^{-1}$ $\cdot$ mmHg), and $30.4 \pm 12.4$ (mmHg), respectively. There were no significant differences in these parameters between DS and control run. The magnitude of $S'_L$ in the control run was larger than that in the DS run.

Table 2 illustrates that in mild hypoxia (from 80 to 50 mmHg in $P_{ETO_2}$), there were no significant differences in the $\dot{V}E$ and $\dot{V}T$ between both the experimental

![Graph](image-url)
runs with and without DS. The respiratory rates were not greatly changed from the DS to the control run. But, in moderate to severe hypoxia (less than 45 mmHg) the magnitude of VE and VT with DS was greater than the control ($p < 0.05$).

Figure 4 illustrates a significant correlation between $\Delta P_{EtO_2.\text{expected}}$ and $\Delta P_{EtO_2.\text{actual}}$.

**DISCUSSION**

The $G_0$, indicated in the present experiment corresponds to the negative value of the open-loop gain designated by MILHORN (1966). He stated that this concept applied to both linear and non-linear functions. $G_0$, and $G_{CO_2}$ are the comparable parameters by definition, because they are similarly the product of both the slopes of the controller and controlled loops. It can be stated that $df(x)/dx$ is the slope of the equation $y = f(x)$ and $dg(y)/dy$ is the slope of the equation $x = g(y)$. Milhorn expressed the open-loop gain in a general form as: $-df(x)/dx \times dg(y)/dy$, which corresponds to the negative value of overall gain.

$G_{O_2}$, the overall gain of the $O_2$-ventilation feedback control system, was found to be progressively elevated as hypoxia progressed. This was in contrast to the $G_{CO_2}$, obtained at normoxia (HONDA et al., 1981, 1983). Individual differences were particularly great in severe hypoxia.

HONDA et al. (1981, 1983) found that $G_{CO_2}$ of normal healthy males was $-16.1 \pm 8.5$ (mean $\pm$ S.D.) and $-17.0 \pm 7.5$, respectively. SEVERINGHAUS (1972) stated that this value was about $-10$. In the present study, the absolute magnitude of $G_{O_2}$ did not exceed that of $G_{CO_2}$ even at the $P_{EtO_2}$ level of 40 mmHg.

From the phylogenetical point of view, DEJOURS (1981) explained that the principal aim for the control of respiration was the adequate oxygenation of the tissues. But the ventilation of human beings as air breathers at sea level is chiefly controlled by $CO_2$ stimulation, because their ventilation is adjusted so as to minimize $CO_2$ accumulation and the concomitant respiratory acidosis under normoxic conditions. With decreasing $P_{EtO_2}$, however, a hypoxia mediated control system gradually becomes predominant. In our subjects, even at the $P_{EtO_2}$ level of 40 mmHg where $G_{O_2}$ did not exceed $G_{CO_2}$, ventilation was considered to be maintained predominantly not by $P_{O_2}$ stimulation, but by $P_{CO_2}$ stimulation.

By adding the external dead space of 250 ml, the $P_{EtO_2}$ decrement was obtained ($\Delta P_{EtO_2.\text{actual}}$). This value was compared with that calculated from $G_{O_2}$ ($\Delta P_{EtO_2.\text{expected}}$). As seen in Fig. 4, $\Delta P_{EtO_2.\text{expected}}$ was not significantly different from $\Delta P_{EtO_2.\text{actual}}$. This was in good agreement with what we found in $\Delta P_{EtCO_2}$ with external dead space in normoxia (HONDA et al., 1983).

OTIS (1964) stated that the oxygen cost of breathing at rest had been found to be in the order of 0.5 to 1.0 ml per liter of ventilation, and it was only a small fraction of the total metabolism. The magnitude of augmented ventilation in the present experiment was at most in the order of 10-20 liters·min$^{-1}$. Therefore,
the resting $V_0$, measured by the Douglas bag method was used in the calculation of $G_0$, throughout the experiments.

It was postulated in the calculation of $SL'$ that the difference between inspired and expired minute volume ($\dot{V}_I$ and $\dot{V}_E$, respectively) was negligible. We have calculated the magnitude of error in $G_0$, caused by this assumption. From the data of subjects Y.H. and Y.S., this value was found to be $0.0023 \pm 0.0018$, which, in fact, was exceedingly smaller than the actual magnitude of $G_0$.

In our experiment, the mean values and standard deviations of $V_D$ in the control run, at $P_{ET_0}$, 80, 60, 50, 45, and 40 mmHg, were $4.72 \pm 1.82$ (liters $\cdot$ min$^{-1}$), $5.22 \pm 1.92$, $5.04 \pm 2.43$, $5.14 \pm 2.34$, and $5.78 \pm 2.82$, respectively. Although $V_D$ slightly increased with decreasing $P_{ET_0}$, no significant increment was found from consecutively high to low $P_{ET_0}$ levels and between 80 and 40 mmHg $P_{ET_0}$ levels. $V_D$ was thus estimated to be a constant value as expressed in Eq. (5).

The mean values and standard deviations of $V_{CO_2}$ in the DS and control run were $246 \pm 45$ (ml $\cdot$ min$^{-1}$) and $221 \pm 26$ (ml $\cdot$ min$^{-1}$), respectively, and those of $V_{O_2}$ were $270 \pm 44$ (ml $\cdot$ min$^{-1}$) and $243 \pm 29$ (ml $\cdot$ min$^{-1}$), respectively. Although no significant difference was seen in $V_{CO_2}$, $V_{O_2}$ in the DS run was larger than that in the control run ($p < 0.05$). However, the difference of the magnitude in $V_{O_2}$ did not result in a significant difference in $G_0$ between the DS and control run.

In Table 2, $SL'$ in the DS run was smaller than in the control run. In both runs, comparison of $SL'$ was made at the same inspired $P_{O_2}$ level, and $P_{ET_0}$, in the DS run was slightly lower than in the control run by the amount of $\Delta P_{ET_0}$ $\cdot$ actual. Accordingly, $SL'$ was slightly less in the DS than in the control run.

Fenner et al. (1968) and Goode et al. (1969) observed that enhanced ventilatory response to CO$_2$ with tube breathing took place in normoxia or when accompanied by hypoxia. This fact was thought to be ascribed to the peculiar time-pattern of the $P_{CO_2}$ signal which possibly influenced the arterial chemoreceptors. The profile of $P_{CO_2}$ change in the airway is such that in the later period of inspiration, $P_{CO_2}$ will drop sharply. If this feature effectively stimulated the peripheral chemoreceptors, enhanced ventilation would have to ensue. Accordingly, actual $P_{ET_0}$ change due to the DS application would have been smaller than the estimated $P_{ET_0}$ change from the $G_0$. Clearly, this was not the case in our experiments, as mentioned above. The amount of DS applied in Fenner et al. and Goode et al. was 1.4 liters which was much larger than the one used by us (250 ml). Such a big difference in the dead space volume may have been responsible for the different results.

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