Alterations in Ventilatory Pattern and Ratio of Dead-Space to Tidal Volume*

Richard W. Baker, M.D.; and N.K. Burki, M.D., Ph.D.

The effects of alterations in ventilatory pattern on the simultaneously measured physiologic and anatomic deadspaces (Vdphys and VDan, respectively) and the dead-space to tidal volume ratio (Vd/Vt) were studied in 17 healthy normal subjects (13 men, four women, ages 21 to 36 years). There were no significant changes in VDan with increases in respiratory frequency (f) or tidal volume (Vt). The Vdphys increased (mean change +0.153 L, p<0.05) with increase in Vt (mean increase +0.84 L, p<0.01), but did not alter significantly with a twofold increase in f, at control Vt.

Increase in Vt significantly reduced Vd/Vt (mean change -10.4 percent, p<0.05), but increase in f, at control Vt, did not significantly alter Vd/Vt. These results indicate that in normal subjects, increase in Vt alters ventilation/perfusion matching in the lungs, whereas an increase in f, at constant Vt, has no effect on ventilation/perfusion matching. Increases in Vd/Vt cannot, therefore, be ascribed to alterations in ventilatory pattern where either Vt, or f, or both are increased.

Measurement of the matching of pulmonary ventilation (V) and perfusion (Q) is an important consideration in the assessment of pulmonary function. One of the classic methods of assessing V/Q distribution is by measurement of the ratio of respiratory dead-space (Vd) to tidal volume (Vt); this measurement provides useful clinical information. However, in clinical medicine, the conditions under which the measurement is made, i.e., the ventilatory pattern, is very variable. Although changes in the absolute respiratory deadspace with various breathing patterns have been described, there have been no systematic studies of the effects of ventilatory pattern changes on Vd/Vt. While studies utilizing techniques for simultaneous anatomic and alveolar deadspace have been published, the effects of changes in ventilatory pattern on simultaneously measured anatomic and physiologic deadspace have not been studied.

The present study was undertaken to examine the effect of changes in ventilatory pattern on Vd/Vt, as well as on the physiologic (Vdphys) and anatomic deadspace (VDan) measurement in healthy, normal subjects.

**METHODS**

A total of 17 healthy, normal, nonsmoking subjects (13 men and four women, age range 21 to 36 years) were studied. Written, informed consent was obtained from each subject.

In each subject, an arterial catheter was positioned in the radial artery at the wrist of the nondominant arm by an aseptic, percutaneous technique. A two-way stopcock was attached to the catheter, and the stopcock-catheter assembly was filled with heparin to prevent clotting. The subject was seated comfortably and breathed via a mouthpiece from a Hans-Rudolph one-way valve (dead-space 18 ml). Pneumotachographs, attached to both the inspiratory and expiratory sides of the valve, provided flow signals via differential pressure transducers (Gould-Statham, PM 15); the flow signals were electronically integrated to volume and recorded on a direct pen writing recorder. In addition, the inspiratory volume signal was displayed on a dual beam oscilloscope placed in full view of the subject. The pneumotachographs were calibrated, against a dry, rolling seal spirometer using a calibrated syringe filled with room air and with a mixture of 5 percent CO2 in air. In addition, the expiratory pneumotachograph was further calibrated against the spirometer while the subject was breathing into the system. Air was sampled at the mouth and analyzed for CO2 concentration on a CO2 analyzer and continuously recorded. The expired gas was collected in a 60-L Douglas bag to which the CO2-analyzed gas was also returned. At the end of each ventilatory pattern measurement, the contents of the Douglas bag were analyzed for gas volume, and CO2, O2, and N2 concentration, using a mass spectrometer. Since both inspiratory and expiratory tidal volumes were recorded, changes in the end-expiratory lung volume could be noted. Each subject performed a few training runs to assure that there were no major shifts in the end expiratory lung volume with the various breathing patterns. During the control period, the subject was allowed to settle into a relaxed breathing pattern before measurements were made. For condition 1, the subject was asked to target a trace on the oscilloscope which displayed double the subject's control Vt at the control breathing frequency. For condition 2, the subject targeted the oscilloscope trace, set at approximately twice the control breathing frequency, at control Vt; for condition 3, both Vt and f were targeted at approximately twice the control values. Between each ventilatory pattern condition, a minimum interval of five minutes was allowed, to permit the subject's end tidal CO2 concentration (PetCO2) to return to control values. During each condition, measurements were only begun after the subject had settled into a stable breathing pattern and the individual breath end-tidal PCO2 (PetCO2) did not vary by more than ±2 mm Hg; in the experimental conditions, this usually required about 45 to 60 s from the initiation of the ventilatory pattern. In eight of these subjects, measurements were also made during condition 4, in which f was further increased above the condition 2 levels, at control Vt. Since the relative position of the jaw and neck are known to alter dead-space volume, particular care was taken to avoid changes in these positions during the study.

The measurements consisted of recording tidal volume and tidal volume.
Alterations in Ventilatory Pattern (Baker, Burd)

Table 1—Measurements in 17 Subjects

<table>
<thead>
<tr>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pH</th>
<th>Vₑ (L/min)</th>
<th>f (min⁻¹)</th>
<th>Vd/Vt, %</th>
<th>Vdphys, L</th>
<th>Vr/Tl, Ls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>100.9 ± 16.1</td>
<td>35.4 ± 5.4</td>
<td>7.43 ± 0.04</td>
<td>10.3 ± 4.0</td>
<td>0.88 ± 0.43</td>
<td>13.3 ± 2.7</td>
<td>± 7.5 ± 0.124</td>
</tr>
<tr>
<td>Condition 1</td>
<td>111.0 ± 25.9†</td>
<td>75.53† ± 20.3‡</td>
<td>17.2‡ ± 12.1</td>
<td>28.4‡ ± 0.49†</td>
<td>0.63‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Vt: 2)</td>
<td>108.2 ± 6.7</td>
<td>7.30 ± 0.04</td>
<td>8.2 ± 0.68</td>
<td>19.47 ± 3.23</td>
<td>0.96‡</td>
<td>39.02</td>
<td>0.317‡</td>
</tr>
<tr>
<td>Condition 2</td>
<td>115.8± 7.66‡</td>
<td>20.47± 1.65</td>
<td>38.1± 3.07</td>
<td>23.01</td>
<td>39.02</td>
<td>0.317‡</td>
<td>0.53‡</td>
</tr>
<tr>
<td>(Vt: 2 + f)</td>
<td>115.8± 7.66‡</td>
<td>20.47± 1.65</td>
<td>38.1± 3.07</td>
<td>23.01</td>
<td>39.02</td>
<td>0.317‡</td>
<td>0.53‡</td>
</tr>
</tbody>
</table>

*All volumes BTPS. PaO₂, PaCO₂, arterial Po₂ and Pco₂ respectively; Vₑ, minute ventilation; Vt, tidal volume; F, respiratory frequency; Vdphys, physiologic deadspace; Vr/Tl, inspiratory flow rate. Significance of difference, Newman-Keuls one-way analysis of variance. p<0.05.†Control.‡Condition 1.¶Condition 2.

CO₂ concentration, with simultaneous collection of the expired gas over a minimum period of 120 s; an arterial blood sample of 10 ml was slowly drawn over a period of 90 s during the expired gas collection. The arterial sample was immediately placed in ice and analyzed, within one minute of withdrawal, for Po₂, Pco₂, and pH. The ratio, Vd/Vt, was calculated from the simultaneously measured arterial Pco₂ (PaCO₂) and mixed expired gas Pco₂ (PeCO₂), using the Enghoff modification of the Bohr equation, and the physiologic dead-space (Vdphys) was calculated. The Vd/Vt was corrected for apparatus dead-space. The CO₂ anatomic dead-space (Vdan) was measured simultaneously with the measurement of Vd/Vt in eight of the 17 subjects. Simultaneous recordings of the expired gas volume and expired CO₂ concentration were digitized using a computer, and the resultant CO₂ concentration-volume relationship was displayed on an X-Y plotter. The instrument and sampling delay for CO₂ was measured before each experiment by presenting a relatively square-wave pulse of 5 percent CO₂ in air, rapidly delivered from a syringe at the mouthpiece. From the resultant simultaneous recordings of expiratory volume and CO₂ concentration, the lag time in the leading edge of the CO₂ concentration deflection, relative to the volume record, was measured; on average, this was about 0.2 s. The computer program included this adjustment for the instrument delay for CO₂ measurement, so that the corrected simultaneous CO₂/ volume plots were displayed. From the plot, another computer-digitized routine was used to measure the dead-space, using the trapezoid rule for defining the equal-area mid-point in phase 2. In the control state, and each experimental condition, at least four CO₂/ volume plots were digitized and the Vdan computed, and the mean value was calculated. The repeatability of the measurement of Vdan by this method in the same subject on consecutive breaths under any given condition was within ±10 ml.

In each subject, at least three forced expiratory spirometers were recorded for measurement of the forced vital capacity and forced expired volume in one second, to confirm normal airway mechanics. Statistical analysis of the significance of difference in the various measurements, among the control state and the various experimental conditions, was performed by Newman-Keuls one-way analysis of variance. Correlation coefficients and partial correlations were calculated by standard methods.

RESULTS

During the various experimental conditions, the end-expiratory lung volume did not change by more than ±250 ml in any individual.

The mean results in the group are shown in Table 1. The minute ventilation increased significantly in all three experimental conditions from the control value; however, it was not significantly different between conditions 1 and 2. Thus, there were significant changes in arterial Po₂, Pco₂, and pH in the three experimental conditions compared to the control state, but the blood gas values were not significantly different between conditions 1 and 2. The ratio Vd/Vt decreased significantly when the tidal volume was doubled, either with or without an increase in respiratory frequency; however, an increase of the respiratory frequency, without a change in tidal volume, did not result in any significant change in Vd/Vt. Similarly, Vdphys increased significantly with increase in tidal volume (conditions 1 and 3), but did not alter significantly from control with an increase in respiratory frequency. That the increase in Vdphys is primarily related to the change in Vt is indicated by the significant correlation (Table 2) between change in Vt and change in Vdphys in the three experimental conditions. The partial correlation coefficients, when considering changes among Vdphys, Vt, and f are significant between Vdphys and Vt, but not between

Table 2—Grouped Correlation Coefficients and Partial Correlations Between Physiologic Dead-Space (Vdphys), Tidal Volume (Vt) and Respiratory Frequency (f) in 17 Subjects

<table>
<thead>
<tr>
<th>Vdphys:Vt</th>
<th>Vdphys:f</th>
</tr>
</thead>
<tbody>
<tr>
<td>r*</td>
<td>t</td>
</tr>
<tr>
<td>Control</td>
<td>0.89</td>
</tr>
<tr>
<td>(n = 17)</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Condition 1</td>
<td>0.78</td>
</tr>
<tr>
<td>Change from control</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Condition 2</td>
<td>0.72</td>
</tr>
<tr>
<td>Change from control</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Condition 3</td>
<td>0.86</td>
</tr>
<tr>
<td>Change from control</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

* is grouped correlation coefficient; t, Student's t-value for partial correlations. In experimental conditions 1, 2, and 3, the correlations and partial correlations refer to changes in Vdphys, Vt, and f from the control values.
Table 3—Measurements in Eight Subjects

<table>
<thead>
<tr>
<th></th>
<th>VT</th>
<th>Vr</th>
<th>f</th>
<th>Vd/Vr</th>
<th>Vp</th>
<th>Voa</th>
<th>PaO2</th>
<th>PaCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8.5</td>
<td>0.53</td>
<td>15.2</td>
<td>39.5</td>
<td>0.22</td>
<td>0.189</td>
<td>88.4</td>
<td>38.9</td>
</tr>
<tr>
<td>n=8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition 1</td>
<td>±2.2</td>
<td>±0.13</td>
<td>±1.4</td>
<td>±7.5</td>
<td>±0.07</td>
<td>±0.026</td>
<td>±7.7</td>
<td>±2.7</td>
</tr>
<tr>
<td>(Vr.2)</td>
<td>17.2†</td>
<td>1.36†</td>
<td>12.9</td>
<td>25.2†</td>
<td>0.34†</td>
<td>0.206</td>
<td>115.5†</td>
<td>26.5†</td>
</tr>
<tr>
<td>Condition 2</td>
<td>±4.1</td>
<td>±0.36</td>
<td>±2.5</td>
<td>±7.2</td>
<td>±0.15</td>
<td>±0.204</td>
<td>±3.9</td>
<td>±2.1</td>
</tr>
<tr>
<td>(f.2)</td>
<td>15.0†</td>
<td>0.63†</td>
<td>23.9†</td>
<td>38.6†</td>
<td>0.25†</td>
<td>0.203</td>
<td>103.9†</td>
<td>30.6†</td>
</tr>
<tr>
<td>Condition 3</td>
<td>±2.9</td>
<td>±0.15</td>
<td>±3.7</td>
<td>±8.6</td>
<td>±0.08</td>
<td>±0.019</td>
<td>±8.8</td>
<td>±4.2</td>
</tr>
<tr>
<td>(Vr.2 + f.2)</td>
<td>28.1††$</td>
<td>1.22††$</td>
<td>22.8††$</td>
<td>29.5††$</td>
<td>0.350††$</td>
<td>0.218</td>
<td>119.1†</td>
<td>22.3†</td>
</tr>
<tr>
<td>Condition 4</td>
<td>±4.4</td>
<td>±0.20</td>
<td>±1.9</td>
<td>±11.9</td>
<td>±0.118</td>
<td>±0.025</td>
<td>±1.7</td>
<td>±4.1</td>
</tr>
<tr>
<td>(Vr.2 + f.2)</td>
<td>17.9†</td>
<td>0.56†</td>
<td>32.8††$</td>
<td>39.6†</td>
<td>0.23†</td>
<td>0.214</td>
<td>107.1†</td>
<td>29.1†</td>
</tr>
<tr>
<td>Condition 5</td>
<td>±5.7</td>
<td>±0.22</td>
<td>±6.2</td>
<td>±7.0</td>
<td>±0.10</td>
<td>±0.057</td>
<td>±7.4</td>
<td>±3.4</td>
</tr>
</tbody>
</table>

*Abbreviations as in Table 1. Significance of difference, Newman-Keul’s one-way analysis of variance, p<0.05.
†Control.
§Condition 1.
$Condition 2.
||Condition 3.

Vdphys and f (Table 2).

Table 3 shows the simultaneously measured values of VDan in eight subjects. There were no significant changes in VDan during the various alterations in ventilatory pattern, whereas significant changes in Vdphys occurred with increase in tidal volume. In addition, in this group further increases in respiratory frequency above the control value (condition 4) also did not significantly alter Vd/Vr from control values.

**DISCUSSION**

Discussions of respiratory dead-space over the past several decades have been bedeviled by unclear definitions. In the present study, we have adhered to currently accepted definitions of dead-space, thus, the anatomic dead-space (VDan), measured by the single breath technique from the expired CO2 concentration-volume trace, is synonymous with the series or airway deadspace. It extends from the lips to the interface, in the respiratory bronchioles, between inspired and alveolar gas. The physiologic dead-space (Vdphys), as measured in the present study by the Enghoff modification of the Bohr technique, consists of the sum of VDan and the alveolar deadspace (Vdalv). Thus, Vdalv includes dead-space from all causes, distal to the inspiratory/alveolar gas interface.

In assessing the present study, it is essential to examine the accuracy of the measurement techniques. For the physiologic dead-space measurements there are two requisites: an equilibrium between the alveolar and end-capillary PCO2 and a simultaneity of arterial and mixed expired gas analysis. These two conditions were met for the present study, since no measurements were begun in any control or experimental condition until the end-tidal PCO2 was varying less than ±2.0 mm Hg, and 10 ml of arterial blood were slowly drawn simultaneously with the collection of expired gas. Under these conditions, errors in the Vd/Vr measurements have been shown to be negligible. The measurement of VDan from the expired CO2 and volume traces is based upon the techniques of Aitken and Clark-Kennedy and Shepard et al. In the present study, VDan measurements in consecutive breaths in any given subject in the control or given experimental conditions did not vary by more than ±10 ml. A further aspect of the present study concerns the constancy of end-expiratory lung volume; as noted, the measured change in end-inspiratory lung volume did not exceed ±250 ml in any individual. However, this figure could be somewhat larger given the difficulties of ensuring accuracy of the pneumotachygraph calibrations and the possible effects of changes in respiratory quotient and water vapor in the lungs.

The effect of changes in ventilatory pattern, particularly changes in Vr on respiratory dead-space, has exercised scientists almost since the concept of pulmonary dead-space was introduced over a century ago by Zuntz. Loewy extended the respiratory dead-space concept to anatomic and physiologic dead-space. The classic argument in respiratory physiology, between Haldane and Priestley and Krogh and Lindhard concerned the very subject of the present study, ie, the effects of changes in Vr on Vd. It became apparent later that Haldane and Priestley were measuring Vdphys, although there were technical inaccuracies related to alveolar gas sampling, whereas Krogh and Lindhard measured VDan, using H2 as the marker gas. When this is taken into account, it is clear from the majority of studies that an increase in Vr results in no significant change in VDan, whereas Vdphys increases markedly. The results of our study, utilizing simultaneous measurement of VDan and Vdphys, are in conformity with previous findings on the effects of changes in Vr on Vdphys and VDan.

The small, nonsignificant increase in VDan with an increase in Vr is in accordance with the findings of Shepard et al; these workers showed that VDan increases with increasing end-inspiratory lung volume.
as would have occurred with increase in VT in conditions 1 and 3 in the present study. However, the data of Shepherd et al also indicate that the change in VDan for an increase in VT of 800 ml, as in the present study, would only be about 16 ml, which is similar to the findings of the present study.

The significant increase in VDphys with increase in VT, in the absence of a significant change in VDan, implies that VDalv must have increased. The increase in VDalv must be due to an increased V/Q mismatch. Although an increase in lung volume has been shown to increase VDphys, and the end-inspiratory lung volume must have increased with increase in VT in condition 1, this degree of increase (mean change in VT = 0.84L) would not be expected to have a significant effect on VDphys. A small degree of inhomogeneity of V/Q exists in normal subjects, and has been suggested to increase with increased inspiratory flow rate. In the present study, the increase in VDphys with increase in VT cannot have been a consequence of the increased inspiratory flow rate alone, since there was no significant change in VDphys with increased respiratory frequency (conditions 2 or 4). Thus, it would appear that the increased VT itself was the primary factor related to the increase in VDphys. A likely cause is probably an increase in ventilation of poorly perfused areas of the lung, resulting in increased V/Q inhomogeneity. The increased V/Q inhomogeneity may also be due to temporal mismatching in that, with an increase in VT, the initial expiratory gas flow rate would be even greater, whereas alveolar capillary blood flow is maximal at the end of expiration, resulting in a temporal mismatch of ventilation and perfusion.

The absence of a significant effect of increased respiratory frequency on either VDan or VDphys is consistent with previous studies of VDan and VDphys.

The ratio VD/VT is a commonly used measurement, useful both in experimental studies and in clinical medicine. However, the effects of variations in ventilatory pattern on VD/VT have not been systematically studied; even so, conventional clinical wisdom assumes that an increase in respiratory frequency results in an increase in VD/VT. The present study indicates that, even with a marked increase in respiratory frequency, VD/VT is not significantly altered. Lifshay et al examined the effects of changes in ventilatory pattern, combined with changes in end-inspiratory lung volume, on Vphys; they did not report the VD/VT values, and insufficient data are presented to assess the effects on VD/VT. Poppius et al found an increase in the arterial to end-tidal PCO2 difference, and by analogy, in VD/VT, with increase in respiratory frequency. However, the increase in f was achieved with no change in alveolar ventilation, and hence, VT must have decreased significantly. Thus, whether the increase in VD/VT was due to the fall in VT alone or in combination with the increase in f, is unclear.

The present study shows that in normal subjects, VDan is unaffected by changes in respiratory frequency and/or tidal volume. The VDphys increases significantly with increase in VT, but increases in f have little effect on VDphys. The ratio VD/VT decreases with increased VT, but is unaltered by changes in f, when VT is kept constant. These findings are of clinical consequence, in that they imply that changes in ventilatory pattern either have no effect on VD/VT (increase in f), or decrease VD/VT (increase in VT); therefore, an increase in the VD/VT ratio, even if associated with increases in f and/or VT, would very likely be due to major nonphysiologic V/Q mismatching. Such an increase in VD/VT, implying a mismatch of V/Q, may be found in pulmonary embolism, pulmonary hypotension, chronic obstructive lung disease, the adult respiratory distress syndrome, etc. Thus, increases in VD/VT can probably not be attributed to ventilatory pattern changes, except perhaps with the unusual combination of an increased respiratory frequency with decreased VT, and a normal or reduced minute ventilation.

ACKNOWLEDGMENT: We are grateful to Mr. Louis Hempel, Mr. Thomas Keener, and Dr. David Smith for their invaluable assistance.

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