LUNG FUNCTION STUDIES. II. THE RESPIRATORY DEAD SPACE1,2

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CERTAIN methods of estimating pulmonary ventilatory efficiency are limited by the accuracy of the measurement of respiratory dead space (1, 2). Krogh and Lindhard measured the physiological dead space and concluded that it varied within narrow limits during changes in lung inflation (3); on the other hand, Haldane and Priestley (4) maintained that the dead space might increase as much as 800 cc. during maximal lung inflation. Though subsequent investigations (5, 6) have in general confirmed the work of Krogh and Lindhard, there still remains considerable uncertainty about the magnitude and constancy of the volume of the respiratory dead space. Within the past few years some investigators have employed a single dead space volume for different tidal volumes (1) whereas others have used two values for dead space, one for shallow and another for deeper breaths (7). The development by Lilly and Hervey (8) of the nitrogen meter, for continuous analysis of the nitrogen concentration of respired gases, has made possible the reinvestigation of this problem.

Since the terminology used by various writers is not uniform, it seems advisable to clarify the meaning of dead space. The respiratory system may be divided into those parts which serve primarily as a conducting airway and not as sites for rapid change of O2 and CO2 (mouth, nose, pharynx, larynx, trachea, bronchi and bronchioles) and those whose chief function is gas exchange (alvcoli, alveolar sacs and atria). If a sharp separation could be made between the two, the former would be defined as the dead space and the latter as the container of alveolar air. If the dead space gas could be expelled from the respiratory tract as a bloc of gas with a sharp boundary line dividing it from the alveolar gas, its measurement would be simplified. However several factors prevent this: first, anatomical studies indicate that the boundary between conducting and exchange airway is not definite; second, diffusion occurs at this boundary area and obscures any sharp margin; third, when the gas is put into motion during expiration, some alveolar gas pushes into the dead space gas and so eliminates a square front. The latter process of expiratory gas mixing

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3 Research Fellow of the American College of Physicians.
The conducting airway must be subject to aerodynamic variables which are independent of the original separation of dead space gas from alveolar gas.

However, it has been found possible, by simultaneous measurement of nitrogen concentration and volume flow of expired gas, to separate dead space gas from alveolar gas by an application of Bohr's formula. Throughout this paper, the term 'physiological dead space' will be used to refer to the volume of the conducting airway down to the location at which a large change in gas composition occurs. This measurement of physiological dead space will change not only with alterations of the caliber of the airway, but also with the extent of boundary diffusion between the alveolar and dead space gases; the latter, among other factors, is a function of time and hence of the rate of respiration.

The effective ventilation of the residual air by a given tidal volume is reduced by the physiological dead space and also by non-uniform ventilation of the residual air. Therefore ineffective tidal volume has these two components; it is believed that the method to be described may differentiate the two.

METHODS

This method is based upon the continuous and simultaneous measurement of
1) expired gas volume-flow and
2) expired gas N₂ content, following the change from breathing air to breathing 99.6 per cent oxygen.

1. N₂ Analysis. The nitrogen meter developed by Lilly and Hervey (8) continuously samples (using about 1.0 cc/sec.), analyzes and records the nitrogen content of constant composition samples with an accuracy from day to day of ± 2 per cent N₂, relative to Haldane analyses. This is an overall accuracy summing errors in sampling methods, measurement of records and setting the instrument. In our instrument the response to a step-wise change in gas composition occurs with a delay of 0.03 to 0.05 second between the time the sample enters the instrument and the time at which the record starts to change; 95 per cent of the final response is attained within an additional 0.03 second and maximal response is attained 0.10 to 0.12 second after the sample enters the instrument. The delay in the final 5% of response may not be instrumental, but due to our inability to produce a completely square gas front.

2. Volume-flow Analysis. Expired gas is passed through a flow meter, which continuously measures the pressure differential across a 400-mesh screen in the flow path, by means of an electrical capacitance manometer (9). Photographic recording of N₂ concentration and flow is made by appropriate oscillograph galvanometer-camera systems. With the flow meter connected as described below, the response to a step-wise change in flow occurs with a starting delay in recording of not more than 0.03 second and maximal response is attained in an additional 0.05 to 0.07 second. The flow meter response is calibrated daily by blowing compressed air through a rotameter to it. Volumes presented hereafter are derived without temperature correction from the rotameter calibrated at 760 mm. Hg and 21.1°C. The area of the flow tracing, as it is deflected from the zero line by an expired breath, can be converted to a volume measurement by measurement with a planimeter or with a squared transparent sheet. The error in volume measurements by this method is
RESPIRATORY DEAD SPACE

±5 per cent; this combines errors in rotameter (±2%), flow meter calibration and record measurement. In tables 1, 2, 3, 4 and 6, the figures for tidal volume represent the average of three successive expirations. Since the various patterns of breathing were maintained for at least 8 to 10 breaths, it is reasonable to assume that the expiratory volumes were not greatly different from inspiratory or tidal volume.

**TABLE 1. PHYSICAL AND RESPIRATORY DATA ON 45 MALE AND 4 FEMALE SUBJECTS**

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEIGHT</th>
<th>WEIGHT</th>
<th>EXP. VOL. TO WASH OUT D.S.¹</th>
<th>PHYSIOL. DEAD SPACE¹</th>
<th>TIDAL VOL.¹</th>
<th>P.S. × 100</th>
<th>RESP/MIN.</th>
</tr>
</thead>
<tbody>
<tr>
<td>yr.</td>
<td>in.</td>
<td>lb.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.4</td>
<td>70.8</td>
<td>161.5</td>
<td>325</td>
<td>156</td>
<td>651</td>
<td>25.9</td>
</tr>
<tr>
<td>S.E. mean (±)</td>
<td>0.9</td>
<td>0.4</td>
<td>3.3</td>
<td>10</td>
<td>4</td>
<td>33</td>
<td>1.1</td>
</tr>
<tr>
<td>S.D. (±)</td>
<td>5.7</td>
<td>3.5</td>
<td>22.3</td>
<td>65</td>
<td>28</td>
<td>222</td>
<td>7.6</td>
</tr>
<tr>
<td>Coeff. variation</td>
<td>22%</td>
<td>3.5%</td>
<td>14%</td>
<td>20%</td>
<td>18%</td>
<td>34%</td>
<td>29%</td>
</tr>
<tr>
<td>Range</td>
<td>19-38</td>
<td>65-77</td>
<td>120-210</td>
<td>207-472</td>
<td>106-219</td>
<td>276-1448</td>
<td>10-43</td>
</tr>
</tbody>
</table>

**TABLE 2. EFFECT OF VOLUNTARY HYPERVENTILATION ON PHYSIOLOGICAL DEAD SPACE**

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>QUIET BREATHING</th>
<th>VOLUNTARY HYPERVENTILATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc.</td>
<td>cc.</td>
</tr>
<tr>
<td>20</td>
<td>636</td>
<td>111</td>
</tr>
<tr>
<td>21</td>
<td>478</td>
<td>157</td>
</tr>
<tr>
<td>22</td>
<td>476</td>
<td>202</td>
</tr>
<tr>
<td>23</td>
<td>628</td>
<td>147</td>
</tr>
<tr>
<td>24</td>
<td>683</td>
<td>179</td>
</tr>
</tbody>
</table>

**TABLE 3. PHYSIOLOGICAL DEAD SPACE IN VOLUNTARY AND EXERCISE HYPERPNEA**

<table>
<thead>
<tr>
<th>SUBJ. NO. 34 (MALE)</th>
<th>SUBJ. NO. 48 (FEMALE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cc.</td>
<td>cc.</td>
</tr>
<tr>
<td>Voluntary hyperventilation</td>
<td>910</td>
</tr>
<tr>
<td>Post-exercise hyperpnea</td>
<td>810</td>
</tr>
<tr>
<td>Quiet breathing</td>
<td>580</td>
</tr>
</tbody>
</table>

3. Other Apparatus. A nose clip and rubber mouthpiece of 2 cm. internal diameter were used. The mouthpiece was connected to a four-way metal valve of 2.1 cm. internal diameter. Instrumental dead spaces were respectively 40 cc. and 60 cc. when room air or oxygen was breathed. Oxygen (99.6% ± 0.1%) was delivered from a high pressure tank through a demand valve designed to operate with
### Table 4. Effect of End-Inspiratory Lung Volume on Physiological Dead Space

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cc.</td>
<td>cc.</td>
<td>sec.</td>
<td>cc.</td>
<td>cc.</td>
<td>sec.</td>
</tr>
<tr>
<td>Max. exp. pos.</td>
<td>440</td>
<td>119</td>
<td>1.3</td>
<td>660</td>
<td>84</td>
<td>2.2</td>
</tr>
<tr>
<td>Normal exp. pos.</td>
<td>580</td>
<td>168</td>
<td>1.7</td>
<td>895</td>
<td>105</td>
<td>2.5</td>
</tr>
<tr>
<td>High insp. pos.</td>
<td>650</td>
<td>233</td>
<td>1.2</td>
<td>830</td>
<td>202</td>
<td>1.1</td>
</tr>
</tbody>
</table>

### Table 5. Effect of Breathholding on Physiological Dead Space

<table>
<thead>
<tr>
<th>Subject</th>
<th>Quiet Breathing</th>
<th>Breathholding</th>
<th>Diff. of mean D.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1</td>
<td>2.0</td>
<td>132</td>
</tr>
<tr>
<td>51</td>
<td>1</td>
<td>1.3</td>
<td>160</td>
</tr>
<tr>
<td>34</td>
<td>1</td>
<td>2.0</td>
<td>168</td>
</tr>
<tr>
<td>48</td>
<td>1</td>
<td>2.5</td>
<td>107</td>
</tr>
<tr>
<td>52</td>
<td>1</td>
<td>2.1</td>
<td>178</td>
</tr>
</tbody>
</table>

### Table 6. Effect of Small Increase of Inspiratory Time on Physiological Dead Space

<table>
<thead>
<tr>
<th>Subject</th>
<th>Type of Respiration</th>
<th>Physiol. D.S.</th>
<th>Tidal Vol.</th>
<th>Insp. Time</th>
<th>Physiol. D.S.</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>a. Fast insp. &amp; exp.</td>
<td>218</td>
<td>1350</td>
<td>1.3</td>
<td>83</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>b. Slow insp. &amp; exp.</td>
<td>135</td>
<td>1350</td>
<td>3.2</td>
<td>83</td>
<td>3.9</td>
</tr>
<tr>
<td>54</td>
<td>a. Fast insp. &amp; exp.</td>
<td>228</td>
<td>770</td>
<td>1.0</td>
<td>50</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>b. Slow insp. &amp; exp.</td>
<td>178</td>
<td>1060</td>
<td>2.5</td>
<td>50</td>
<td>1.5</td>
</tr>
<tr>
<td>55</td>
<td>a. Fast insp. &amp; exp.</td>
<td>220</td>
<td>1130</td>
<td>1.4</td>
<td>70</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>b. Slow insp. &amp; exp.</td>
<td>150</td>
<td>1160</td>
<td>2.0</td>
<td>70</td>
<td>1.5</td>
</tr>
<tr>
<td>34</td>
<td>a. Regular rhythm</td>
<td>172</td>
<td>572</td>
<td>1.1</td>
<td>61</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>b. Short insp. pause</td>
<td>116</td>
<td>544</td>
<td>3.8</td>
<td>61</td>
<td>2.7</td>
</tr>
<tr>
<td>48</td>
<td>a. Regular rhythm</td>
<td>100</td>
<td>765</td>
<td>1.0</td>
<td>24</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>b. Short insp. pause</td>
<td>76</td>
<td>740</td>
<td>3.8</td>
<td>24</td>
<td>1.9</td>
</tr>
</tbody>
</table>
low inspiratory resistance. Expired gas was conducted through the four-way valve, a Sadd valve and 30 inches of flexible rubber tubing with 2 cm. internal diameter to the flow meter.

The sampling needle of the nitrogen meter was inserted into the middle of the mouthpiece lumen just external to the subject's lips, adding an apparatus expiratory dead space of 2 to 3 cc. Since measurements of physiological dead space were made during expiration, no apparatus correction was made.

Subjects sat quietly in a chair and breathed room air through the mouthpiece for several minutes. The oxygen system was flushed and, during an expiration, the room air orifice was closed so that oxygen was breathed on the following inspiration and thereafter.

4. Subjects. The subjects were healthy white males and females between the ages of 19 and 38 years. Certain physical characteristics are given in table 1.

5. Analysis of Records. Figure 1 shows the type of record obtained when oxygen is breathed after breathing room air. During inspiration, oxygen (0.4% N2) is inhaled. The expired gas may be divided into three nitrogen-fraction phases (8); the first part, approximately 20 to 100 cc. of oxygen and water vapor, represents inspired gas remaining in the upper respiratory tract; a final portion with relatively constant N2 content probably represents 'alveolar' gas; a mid-portion of about 100 to 300 cc. of gas with a rapidly rising N2 content represents a mixture of pure inspired gas and alveolar gas, the mixing presumably being accomplished by boundary diffusion and by expiratory flow conditions in the upper airway.

From the nitrogen and flow curves one can obtain the data to solve Bohr's formula for dead space:

\[ V_e \times C_e = (V_e - V_d) C_a + V_d \times C_i \]

in which

- \( V_e \) = Volume of expired air.
- \( C_e \) = Concentration of a gas in \( V_e \).
- \( V_d \) = Volume of the dead space.
- \( C_a \) = Concentration of the same gas in alveolar air.
- \( C_i \) = Concentration of the same gas in inspired air.

This states that an expired breath consists of a mixture of two parts, each with a definite concentration of a given gas. \( V_e, C_i \) (approximately zero for N2) and \( C_a \) (the N2 concentration of the alveolar phase) may be measured directly from the record. \( C_e \) is obtained by correcting the N2 curve for flow variations and measuring the area under it, thus obtaining volume of N2 expired; this is divided by total volume expired, \( V_e \), to give \( C_e \). The equation may then be solved for dead space. Measurements made in this way will be called 'calculated' physiological dead space.

The factor of non-uniformity of alveolar gas is eliminated as follows: The O2 remaining in the conducting airway after inspiration is mixed in the airway on expiration with alveolar gas similar to that expired immediately after the dead space has been washed out. The N2 concentration of this alveolar gas is measured and inserted in Bohr's formula. Similarly \( V_e \) is taken as the volume expired up to the point at which this initial alveolar concentration is reached. If the N2 content of alveolar gas is uniform, i.e. the alveolar plateau is flat, the same result is obtained if
any volume concentration point is selected after the dead space has been washed out. If the N₂ content of alveolar gas is not uniform, the use of a volume-concentration point early in the alveolar plateau largely eliminates the effects of uneven alveolar N₂ content. This point is selected by drawing a straight line along the top of the alveolar plateau and extending it to the left. The point at which the rising N₂ curve first touches this line is taken for measurement of the alveolar concentration.⁴

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⁴ Records of normal subjects show, in practically all cases, an approximately rectilinear plateau; in some subjects with pulmonary disease the plateau is curved and the initial alveolar point cannot be selected in this way.
Bohr equation also equals the sum of the two products, $V_{ds} \times C_i$ and $C_a \times (V_e - V_{ds})$. Since $C_i$ lies on the abscissa, $V_{ds} \times C_i$ contributes no area. Therefore the area under the curve equals $C_a \times (V_e - V_{ds})$. $C_a$ is known, and $V_e - V_{ds}$ may be found by constructing a rectangle which has $C_a$ as one side and which has an area equal to that area under the curve. This is done by dropping a perpendicular to the abscissa such that area A equals area B.

In applying this procedure to the photographic record, a perpendicular is drawn on the nitrogen meter record such that area A equals area B, as in figure 2. This is estimated visually with the help of a squared transparent ruler. The perpendicular is extended to cross the flow curve. The area of the flow curve to the left of the perpendicular is measured, converted to cc. and is called the 'estimated' physiological dead space.

**POTENTIAL SOURCES OF ERROR IN METHODS**

1. *Instrumental Delay.* Figure 3 shows an expiratory record (above) and a record obtained with a stepwise change in flow and N2 content (below). With quiet or rapid expiration, the change of N2 concentration occurs over a period considerably longer (4- to 8-fold and 2- to 4 fold respectively) than the instrumental delay. Likewise the sustained high level of expiratory flow rates is attained only after a delay several times longer than the instrumental lag. Therefore the analyses of N2 and flow should be reasonable representations of the actual events.

2. *The 'estimation' method* assumes arithmetic scales on the ordinate and abscissa of figure 2. The non-arithmetic scale of the nitrogen meter response (fig. 1) should make the estimations about 5 per cent too large. Flow variations which occur during the period of rapid N2 change may introduce error. Actually those flow variations are small because a) more than 75 per cent of peak flow is attained early in expiration, before N2 beings to rise rapidly, and b) the apparatus has a damping effect. The 'calculation' method is not subject to these errors. Therefore comparison was made between the values obtained by 'calculation' and by 'estimation' in 14 different breaths including quiet and rapid expirations performed by 6 subjects. Estimated values varied both above and below the calculated values. The mean difference between estimated and calculated was 3.4 cc. and the standard error of the mean
difference was $\pm 2.6$ cc., indicating that there was no significant difference between values obtained by the two methods.

Further checks on the 'estimation' method were made as follows: a) artificial dead spaces were made by connecting rubber hoses to the apparatus mouthpiece, filling the hoses with oxygen and then flushing them through the apparatus with air or gas mixtures containing 63 per cent N$_2$-37 per cent O$_2$, or 58 per cent N$_2$-42 per cent O$_2$, at flow rates of 15 to 35 l/min. The internal volume of the hoses was measured by filling with water. Three estimations of an 85-cc. smooth bore hose, 2.0-cm. internal diameter, were 89, 93 and 82 cc. Four estimations of a 170-cc. corrugated hose, internal diameter 2.0 to 3.0 cm., were 175, 164, 160 and 175 cc. Six estimations of a 205-cc. corrugated hose were 197, 194, 194, 213, 203 and 206 cc. b) Physiological dead space of a subject was estimated to be 168 cc. Then an additional 200 cc. of dead space was added by placing a smooth bore hose in the mouth. Estimations were found to be 373 and 358 cc., differences of 205 and 190 cc.

From the evidence above, it appears that the 'estimation' method, which is technically much easier, is as suitable as the 'calculation'. The data presented here-

### Table 7. Effect of Varying Inspiratory Volume-Flow on Physiological Dead Space

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>PRE-INSPIRATORY POSITION</th>
<th>END-INSPIRATORY POSITION</th>
<th>INSPIRATORY VOL.</th>
<th>INSPIRATORY TIME</th>
<th>MEAN INSPIRATORY FLOW</th>
<th>PHYSIOLOGICAL D.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Max. exp.</td>
<td>Max. exp. + 1700 cc.</td>
<td>1760</td>
<td>1.7</td>
<td>1040 cc/sec.</td>
<td>169 cc.</td>
</tr>
<tr>
<td></td>
<td>Normal exp.</td>
<td>Max. exp. + 1750 cc.</td>
<td>600</td>
<td>1.5</td>
<td>400 cc/sec.</td>
<td>176 cc.</td>
</tr>
<tr>
<td>30</td>
<td>Max. exp.</td>
<td>Max. exp. + 1570 cc.</td>
<td>1570</td>
<td>1.2</td>
<td>1300 cc/sec.</td>
<td>178 cc.</td>
</tr>
<tr>
<td></td>
<td>Normal exp.</td>
<td>Max. exp. + 1870 cc.</td>
<td>625</td>
<td>1.2</td>
<td>520 cc/sec.</td>
<td>188 cc.</td>
</tr>
</tbody>
</table>

---

1 All figures average of three breaths.
measurements on three successive similar breaths. The standard error of these
means is \( \pm 5.1 \) cc., the standard error of the difference between two means is \( \pm 7.2 \) cc. and a difference of 20 cc. or more is significant.

RESULTS

1. The volume of gas required to wash out the dead space on expiration, after
which 'alveolar' gas is expired, is shown in table 1 to have an average value of 325 cc. Figure 2 shows that this volume, tentatively called 'kinetic dead space' by Lilly (8), is larger than that of the physiological dead space, since it includes both the pure inspired gas remaining in the airway after inspiration and also some alveolar gas, which is mixed in the airway with inspired gas during expiration.

2. Some alveolar gas appeared in the expired air, as shown by the start of a
rising \( N_2 \) content, after an average of 41 cc. expired by subjects in table 1. The accuracy of this measurement is limited by the flow meter lag and by the relative insensitivity of this \( N_2 \) meter at very low \( N_2 \) fractions.

3. Table 1 shows the volume of the physiological dead space found in 45 normal
men, sitting and breathing naturally. The average is 156 cc. with an 18 per cent coefficient of variation. Measurements in 4 women gave smaller values, averaging 104 cc.

4. Radiologic and bronchoscopic evidence has shown that the bronchial tree
increases in volume with inspiration. Thus, anatomical changes could affect the
volume of the physiological dead space. Also the demarcation of gas concentrations
between the terminal bronchioles and the alveolar spaces must be affected by dif-
fusion. The effects of these two factors were shown in the following experiments.

A. Anatomical effects. Measurements made on 5 men, during quiet breathing and during
voluntary hyperventilation, are shown in table 2. Large increases in tidal volume resulted in in-
creases of 46 to 95 cc. in physiological dead space. A comparison of voluntary hyperventilation
and hyperpnea due to exercise (one minute after knee bends) was made in 2 subjects. Table 3
shows that there was no significant difference between the increased physiological dead space found
with the two types of hyperpnea. In view of Verzar's data on changes in total lung volume during
and after exercise (20), it is possible that different results would have been obtained on measure-
ments during exercise, which were precluded by apparatus immobility. The significance of the
notation of inspiratory time in table 3 will be discussed below.

The increased physiological dead space found with larger tidal volumes is presumably due to
the increase in anatomical volume on deeper inspiration. Further demonstration was obtained by
experiments on 2 subjects in whom oxygen inhalation was started at a) maximal expiratory position,
b) normal quiet expiratory position and c) almost maximal inspiratory position. The maximal
differences in end-inspiratory lung volumes were 3000 to 3500 cc.; tidal volume and rate were volun-
tarily made similar at all three lung positions. Table 4 shows that at reduced lung volumes the
physiological dead space was definitely decreased. With an increase of about 3000 cc. in lung vol-
ume, the physiological dead space increased about 100 cc.

B. Diffusion effects. Experiments were made on 5 subjects in which the time available for
diffusion of \( N_2 \) between terminal bronchioles and the more peripheral spaces was prolonged by hold-
ing the breath for about 20 seconds in the normal inspiratory position. Table 5 shows a definite
decline in physiological dead space with breathholding in every case, presumably because the
peripheral boundary of pure inspired gas had receded up the bronchial tree.

In 3 male subjects, diffusion time was varied within physiological limits by voluntarily breath-
ing with a) rapid inspiration and expiration and b) slow inspiration and expiration. In 2 subjects,
breaths with a short end-inspiratory pause were alternated with uninterrupted breaths. Table 6 shows that the physiological dead spaces were smaller with the slow rate and that 2- to 3-second inspiratory pauses also resulted in a decrease.

5. To test the proposal (5) that physiological dead space is decreased by higher rates of inspiratory flow, experiments were done on 2 subjects in which inspiratory time and end-inspiratory lung volume were constant, but the rate of inspiratory volume flow was varied. This was accomplished by analyzing breaths which ended at similar inspiratory positions but started at varying expiratory levels. Inspired volumes were measured on a 6 L. recording spirometer used for the source of O₂. Table 7 shows that increasing the mean inspiratory volume flow by about 2.5 times did not significantly affect the volume of physiological dead space.

**DISCUSSION**

Since the physiological dead space may change in any one individual with respiratory rate and depth, a 'normal' value for a group with varying rates and depths of respiration, and varying anatomy, is not very meaningful. However the average value of 156 cc. for resting males agrees closely with the commonly accepted value of 150 cc. and the 104-cc. average for 4 females is similar to Lindhard's average value of 92 cc. for 5 females. On the other hand, Kaltrieder et al. (11) found an average value of 256 cc. in a group of 50 males, 38 to 63 years old; if the non-uniformity of alveolar ventilation is increased in older 'normal' males (1), a larger value would be expected when calculations are based on Haldane-Priestly alveolar air samples. The method described in this paper has the advantages of knowing the concentration of alveolar gas which immediately follows that alveolar gas which washes out the dead space and of not requiring the cooperation of the subject in obtaining a sample of alveolar gas. It is probable that these factors are partly responsible for the smaller coefficient of variation in this group (18%) as compared to that in Kaltrieder's series (43.5%).

A recent text (12) illustrates the calculation of alveolar ventilation with a) a dead space of constant volume and b) a constant dead space/tidal volume fraction. Our data show that dead space volume is not constant; also it is a variable fraction both of tidal volume in different individuals and of different tidal volumes in one person.

Many authors have found that physiological dead space increases with increasing lung volume. However, in our experiments, the increase from maximal expiratory position to maximal inspiratory position was only of the order of 100 to 150 cc., as Krogh (3) and others (6, 13) have also found. Combining the anatomical data of Rohrer (14) and the radiological data of Huizinga (15), one can calculate that the volume of the airway, from the glottis to the intralobular bronchioles of the fifth order, would increase by about 230 cc. from deep expiration to deep inspiration. The smaller increase measured by physiological methods may perhaps be explained by the time that elapses between the first exposure, during early inspiration of inspired gas in the bronchioles, to the gas of alveolar ducts and alveoli and the exit and analysis of this gas on the succeeding expiration. During this time, diffusion exchange will occur between the bronchioles and the alveoli and the dead space measured by physiological methods will be smaller than the anatomical volume.
Henderson et al. (16) and Haldane (17) found that the dead space for CO₂ and O₂ decreased if the breath was held after inspiration; Grosse Brockhoff and Schoedel (5) were unable to confirm this. Krogh and Lindhard (3) and Mundt (6), using hydrogen methods, noted a decrease but it is doubtful if results obtained with such a rapidly diffusing gas should be applied to the normal respiratory gases. Our data show that prolongation of inspiratory time by only two seconds, such as may result from a prolonged inspiration, will decrease significantly the physiological dead space. Thus with deep slow respiration, the anatomical increase will be counteracted by the prolonged time available for diffusion between the terminal bronchioles and the alveoli. The finding that a 20-second prolongation of inspiratory time (table 5) does not reduce the physiological dead space a great deal more than a two- to four-second prolongation (table 6) is not surprising. In the respiratory bronchioles, for example, the diffusion course is short and only a few seconds or less are required to greatly reduce initial concentration differences (19). The effect of diffusion in the larger bronchioles will be less evident because their total volume becomes progressively smaller toward the large bronchi; also as diffusion courses become longer, time must be prolonged exponentially to accomplish similar degrees of concentration equalization.

Our finding that physiological dead space is unaffected by increased inspiratory volume flow does not support Grosse-Brockhoff and Schoedel's proposal that bronchiolar-alveolar mixing is facilitated by turbulence resulting from faster inspiratory flow, with a resulting reduction of dead space volume. While it cannot be said that turbulent flow and attendant mixing do not occur, diffusion alone should accomplish mixing between the main stream and the alveoli along the respiratory bronchioles and alveolar ducts because the distances involved are so small in relation to normal respiratory times.

The measurements of respiratory dead space by the method described may have several clinical uses: a) patients with pulmonary abnormalities may have large ineffective tidal volumes (2, 18); this method may be able to demonstrate whether an enlarged physiological dead space or uneven intrapulmonary gas mixing is responsible. b) It may be possible to employ the method to measure physiological or pharmacologically induced changes in bronchiolar caliber.

SUMMARY

1. Physiological dead space was measured by simultaneous and continuous measurement of volume flow and N₂ content of gas expired following the change from breathing air to breathing 99.6 per cent O₂. In normal subjects the effect of non-uniform alveolar gas on dead space measurements can be largely eliminated.

2. The average volume of the physiological dead space in 45 healthy males at rest was 156 cc.; the average expired volume required to wash out the dead space was 325 cc. The physiological dead space/tidal volume fraction averaged 25.9 per cent, but varied widely in different individuals.

3. The volume of the physiological dead space is affected by: a) anatomical volume of the bronchial tree. Maximal variations of inspiratory lung volume changed dead space by about 100 cc. Voluntary hyperventilation and post-exercise hyperpnea increased physiological dead space equally; the increase was 100 cc. or
less. b) Gas diffusion between terminal bronchioles and alveolar spaces. Prolongation of inspiratory time by two to three seconds significantly reduced the volume of the physiological dead space and breathholding, during inspiration (20 sec.), caused reductions of 44 to 82 cc. In slow deep breathing the anatomical volume increase is counteracted by diffusion occurring during the prolonged inspiratory time.

4. Variations in the rate of inspiratory volume flow did not affect the volume of the physiological dead space.

5. Clinical applications of the method are suggested.

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