Effect of Exercise on Dilution Estimates of Extravascular Lung Water and on the Carbon Monoxide Diffusing Capacity in Normal Adults

By Carl A. Goresky, J. Wayne Warnica, John H. Burgess, and Brita E. Nadeau

ABSTRACT

Previous studies in exercising animals have demonstrated that the extravascular lung water accessible to measurement by dilution methodology increases in the transition from rest to low-level exercise and thereafter does not change with progress to high-level exercise. In normal humans, similar systematic examination is essential to provide a background for the interpretation of changes in measured extravascular lung water in pathophysiological states. Moreover, such an examination might provide new insight into the mechanisms underlying the change in the pulmonary diffusing capacity with exercise. We therefore measured both the pulmonary extravascular lung water (by use of the triple indicator-dilution technique) and the diffusing capacity for carbon monoxide in 11 subjects, seated on an exercise bicycle, at rest and usually during two levels of exercise. The central blood volume increased by 50% with a tripling of the cardiac output. The accessible lung water increased from an average of 2.16 g/kg to 2.55 g/kg in the transition from rest to low-level exercise, but it did not increase further at the higher level of exercise. The simultaneously measured diffusing capacity for carbon monoxide (single breath and steady state) continued to increase over the whole range of cardiac outputs. We infer that the proportion of the pulmonary parenchyma perfused by blood flow increases slightly in the transition from rest to low-level exercise but increases no further at the higher level of exercise. The continued increase in the pulmonary diffusing capacity over the range in which the estimated lung water values do not change appears to imply that part of this increase may be blood flow dependent rather than dependent on the recruitment of additional surface for exchange.

The alveoli of the lungs are a set of gossamer structures facilitating the exchange between alveolar air and pulmonary capillary blood. In each alveolus, the capillary net, a continuous hexagonal array, is enveloped by two approximating sheets of alveolar septal cells with sparse connective tissue interspersed between. The permeability and the dimensions of the barriers between capillary blood and alveolar air are such that equilibration of gases between the blood and gas phases is facilitated, and the dimensions of the alveolar wall or sheet are such that labeled water would be expected to be distributed from capillary blood into the substance of the sheet in a flow-limited fashion. It has been proposed that at rest, in the pulmonary parenchyma, the gravitational gradient induces a gradient in perfusion which increases from above downward. However, it is thought that during exercise the upper parts of the lungs become better perfused. The pulmonary diffusing capacity increases during exercise, and it has commonly been supposed that the increase is brought about by a recruitment of alveolocapillary surface—by a delivery of flow to areas that are not perfused at rest. In other organs, such recruitment is easy to visualize, since it only implies the start of flow in long tubular capillaries in which there has previously been stasis. In the lungs, however, the flow in the continuous capillary bed of the alveolus is very different: when viewed from the alveolar surface, blood appears to be flowing in a continuous vascular sheet, interrupted only by regularly spaced endothelium-covered posts that connect the two lined alveolar surfaces. Recruitment in this organ therefore might be expected to involve a whole alveolar sheet rather than single pathways within this labyrinth.

We therefore chose to study the phenomena that occur during exercise in upright man by simultaneously measuring the extravascular lung water and the pulmonary diffusing capacity for carbon monoxide. If recruitment occurs in the expected manner, it should be mirrored by increases in both
quantities. If the measured extravascular lung water does not continue to increase with the carbon monoxide diffusing capacity as the level of exercise is increased, it may be appropriate to reformulate our ideas bearing on capillary recruitment or to seek explanations other than capillary recruitment as the basis for the increase in carbon monoxide diffusing capacity with exercise.

Methods

Eleven normal physicians, 9 male and 2 female, between 21 and 30 years of age were studied after informed consent had been obtained. A prerequisite for study was a lack of history of cardiorespiratory disease and a completely normal physical examination, chest X ray, electrocardiogram, hemoglobin, and hematocrit.

The day prior to study, pulmonary function studies were carried out on the subjects. The vital capacity (VC), expiratory reserve volume (ERV), timed vital capacity, and maximum midexpiratory flow rate (measured with a Stead-Wells spirometer) were determined. In addition, the functional residual capacity (FRC) and the airway resistance were measured in a Collins body plethysmograph by the method of Dubois et al. (11). The total lung capacity (TLC) was then calculated from the relation:

\[ TLC = VC + (FRC - ERV) \]

In addition the subjects were pretested on a bicycle ergometer to determine their exercise capability and trained in the maneuvers that would be required of them during an actual experiment.

Experimental Protocol.—On the day of an experiment, each subject was prepared in the following fashion. A 15-gauge catheter was passed percutaneously via the median basilic vein to the superior vena cava and kept patent with a slow heparinized saline infusion. A small polyethylene catheter (PE 60) was inserted percutaneously into the left brachial artery using the Seldinger technique. The subject was then seated on a bicycle ergometer (Warren E. Collins Inc.) and kept at rest for 15 minutes to allow the cardiovascular responses to these manipulations to stabilize. At the end of this time, the subject was still at rest, the single-breath pulmonary diffusing capacity for carbon monoxide was measured by the method described by Ogilvie et al. (12). The gas mixtures inspired consisted of carbon monoxide (0.3%) and neon (0.4%) in room air. A Hans Rudolf high-velocity valve and a Beckman infrared analyzer and for oxygen and carbon dioxide in a Haldane apparatus.

The samples obtained during the indicator-dilution studies were analyzed as follows. Standards were prepared from the injection mixture by addition, in serial dilution, of blood obtained prior to the first study. An aliquot of each sample or standard was diluted with saline, centrifuged, and then assayed in an automatic dual-channel well-type scintillation-crystal gamma ray spectrometer for gamma rays of the appropriate energy. The activity due to each species was determined by use of the data arising from \( ^{51} \text{Cr} \)-labeled red cell and \( ^{125} \text{I} \)-labeled albumin standards. The supernatant fluid was deproteinized with ethanol, and its tritium activity was determined in a liquid scintillation counter. With this method of sample preparation, small amounts of \( ^{51} \text{Cr} \) and \( ^{3} \text{H} \) activity are carried over into the samples assayed in the liquid scintillation counter and contribute in small proportion to the apparent tritium activity. Corrections were made for this phenomenon by use of the data obtained from the \( ^{51} \text{Cr} \)-labeled red cell and \( ^{125} \text{I} \)-labeled albumin standards.

Results

The chief aim of this study was to define the manner in which estimates of extravascular lung water does not continue to increase with the carbon monoxide diffusing capacity as the level of exercise is increased, it may be appropriate to reformulate our ideas bearing on capillary recruitment or to seek explanations other than capillary recruitment as the basis for the increase in carbon monoxide diffusing capacity with exercise.
EXTRAVASCULAR LUNG WATER AND CO DIFFUSING CAPACITY

381

water and pulmonary carbon monoxide diffusing capacity change with exercise. The physiological data describing the background characteristics of each subject are given in Table 1.

The Multiple Indicator-Dilution Studies.—Figure 1 illustrates a typical dilution study. To provide a basis for comparison between the outflow curves for each of the three indicators, the measured activity was expressed as a fraction of the total activity injected per milliliter of blood, that is, as an outflow fraction per milliliter. The outflow fraction per milliliter for the labeled red cells was highest in the first samples, reached the highest and earliest peak, and decayed most quickly. The albumin curve was slightly lower on the upslope, reached a slightly lower and later peak, and decayed only slightly less quickly. The labeled water curve was relatively displaced from the closely aligned curves of the two vascular indicators. Its upslope was delayed, its peak was substantially lower and later, and its downslope decayed substantially slower.

The parameters arising from the rest and exercise studies are displayed in Table 2. The dilution curves were corrected for label recirculation by linear extrapolation of the downslope on a semilogarithmic plot according to the classical method of Hamilton et al. (17). The average extrapolated recoveries of the three indicators were essentially equivalent. For the 31 runs carried out, the ratio of the area under the labeled albumin curve to that under the labeled red cell curve was 1.022 ± 0.054 (SD), and the ratio of the area under the labeled water curve to that under the labeled red cell curve was 1.001 ± 0.084 (SD). The deviation of the latter ratio from unity was random at all three levels of exercise, but the degree of variation became larger as the flow increased. This finding appears to indicate an increased phasic respiratory variation in flow at the higher exercise levels (18). For the purpose of our calculations, the area values under the curves for the two vascular indicators were averaged in any given experiment, and this average value was used to estimate flow. Mean transit times were calculated from the primary dilution curves (19) and corrected for input and output delays, as outlined earlier in this paper, to provide single-passage superior vena cava–brachial artery transit times.

**TABLE 1**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Surface area* (m²)</th>
<th>Hemoglobin (g/100 ml)</th>
<th>Total lung capacity (liters)</th>
<th>Vital capacity (liters)</th>
<th>Functional residual capacity (liters)</th>
<th>Forced expiratory volume (1 second) (liters)</th>
<th>Airway resistance† (cm H₂O/ liters sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>29</td>
<td>177</td>
<td>78.6</td>
<td>1.96</td>
<td>15.6</td>
<td>6.19</td>
<td>5.45</td>
<td>2.26</td>
<td>4.17</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>30</td>
<td>183</td>
<td>80.9</td>
<td>2.03</td>
<td>15.0</td>
<td>7.86</td>
<td>6.38</td>
<td>4.01</td>
<td>4.98</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>28</td>
<td>175</td>
<td>81.8</td>
<td>1.98</td>
<td>16.2</td>
<td>6.82</td>
<td>5.80</td>
<td>3.21</td>
<td>4.25</td>
<td>0.78</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>25</td>
<td>181</td>
<td>77.3</td>
<td>1.98</td>
<td>14.5</td>
<td>7.34</td>
<td>6.18</td>
<td>3.45</td>
<td>4.48</td>
<td>0.61</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>28</td>
<td>170</td>
<td>64.1</td>
<td>1.74</td>
<td>14.5</td>
<td>5.40</td>
<td>4.08</td>
<td>2.69</td>
<td>3.07</td>
<td>1.41</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>28</td>
<td>159</td>
<td>59.0</td>
<td>1.61</td>
<td>12.7</td>
<td>5.13</td>
<td>3.85</td>
<td>2.11</td>
<td>2.80</td>
<td>1.69</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>28</td>
<td>173</td>
<td>67.3</td>
<td>1.80</td>
<td>13.6</td>
<td>6.14</td>
<td>5.02</td>
<td>2.69</td>
<td>2.88</td>
<td>2.11</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>26</td>
<td>180</td>
<td>84.0</td>
<td>2.04</td>
<td>13.8</td>
<td>8.27</td>
<td>6.19</td>
<td>3.10</td>
<td>4.00</td>
<td>1.19</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>29</td>
<td>173</td>
<td>70.5</td>
<td>1.84</td>
<td>14.6</td>
<td>6.18</td>
<td>5.57</td>
<td>2.99</td>
<td>3.69</td>
<td>0.92</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>23</td>
<td>188</td>
<td>82.8</td>
<td>2.10</td>
<td>14.5</td>
<td>7.62</td>
<td>6.34</td>
<td>3.72</td>
<td>5.10</td>
<td>0.64</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>25</td>
<td>170</td>
<td>69.0</td>
<td>1.80</td>
<td>14.3</td>
<td>5.17</td>
<td>4.47</td>
<td>2.18</td>
<td>3.94</td>
<td>1.20</td>
</tr>
</tbody>
</table>

* The surface area was computed according to the nomogram from reference 15.
† The airway resistance was measured by use of the method outlined in reference 16.

Circulation Research, Vol. 37, September 1975
### TABLE 2

**Rest and Exercise Data**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean transit times</th>
<th>Vascular resistance (mmHg)</th>
<th>Arterial blood</th>
<th>Partial pressure of oxygen (mm Hg)</th>
<th>Partial pressure of CO2 (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(seconds)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Rest</td>
<td>13.63</td>
<td>14.25</td>
<td>17.59</td>
<td>1.001/1.024</td>
<td>4.63/0.98</td>
<td>1077</td>
</tr>
<tr>
<td>I 7.91</td>
<td>8.35</td>
<td>9.83</td>
<td>1.119/1.093</td>
<td>8.45/1.79</td>
<td>1148/191.6/38.6</td>
<td>19.2</td>
</tr>
<tr>
<td>2 Rest</td>
<td>12.48</td>
<td>13.09</td>
<td>15.58</td>
<td>1.096/0.962</td>
<td>4.32/0.89</td>
<td>925</td>
</tr>
<tr>
<td>I 7.39</td>
<td>7.82</td>
<td>9.12</td>
<td>1.012/0.996</td>
<td>10.18/2.10</td>
<td>1296/204.7/34.5</td>
<td>24.0</td>
</tr>
<tr>
<td>II 5.39</td>
<td>5.87</td>
<td>6.52</td>
<td>1.151/1.032</td>
<td>17.39/3.58</td>
<td>1642/199.4/40.7</td>
<td>27.4</td>
</tr>
<tr>
<td>3 Rest</td>
<td>19.37</td>
<td>19.95</td>
<td>22.01</td>
<td>1.008/0.908</td>
<td>4.47/0.91</td>
<td>1467</td>
</tr>
<tr>
<td>I 7.33</td>
<td>7.71</td>
<td>9.04</td>
<td>1.059/1.075</td>
<td>10.76/2.19</td>
<td>1351/218.3/36.9</td>
<td>22.9</td>
</tr>
<tr>
<td>II 5.74</td>
<td>6.17</td>
<td>7.01</td>
<td>1.005/1.003</td>
<td>15.68/3.19</td>
<td>1560/216.3/36.4</td>
<td>20.6</td>
</tr>
<tr>
<td>4 Rest</td>
<td>14.09</td>
<td>14.97</td>
<td>17.94</td>
<td>0.996/1.056</td>
<td>3.92/0.85</td>
<td>952</td>
</tr>
<tr>
<td>I 6.07</td>
<td>6.58</td>
<td>7.68</td>
<td>1.043/1.171</td>
<td>12.22/2.63</td>
<td>1293/217.5/47.3</td>
<td>73.6</td>
</tr>
<tr>
<td>II 5.27</td>
<td>5.55</td>
<td>6.25</td>
<td>1.016/1.144</td>
<td>14.97/3.23</td>
<td>1350/170.0/52.7</td>
<td>30.4</td>
</tr>
<tr>
<td>5 Rest</td>
<td>10.46</td>
<td>11.00</td>
<td>12.28</td>
<td>0.933/0.966</td>
<td>4.50/1.17</td>
<td>810</td>
</tr>
<tr>
<td>I 5.42</td>
<td>5.85</td>
<td>6.86</td>
<td>1.016/0.852</td>
<td>11.31/2.94</td>
<td>1069/184.8/39.9</td>
<td>20.7</td>
</tr>
<tr>
<td>II 4.44</td>
<td>4.69</td>
<td>5.40</td>
<td>0.912/0.776</td>
<td>15.53/4.04</td>
<td>1189/173.2/48.4</td>
<td>31.5</td>
</tr>
<tr>
<td>6 Rest</td>
<td>9.62</td>
<td>10.20</td>
<td>12.34</td>
<td>1.057/1.007</td>
<td>4.64/1.31</td>
<td>772</td>
</tr>
<tr>
<td>I 3.85</td>
<td>4.10</td>
<td>4.89</td>
<td>1.064/0.907</td>
<td>11.62/3.28</td>
<td>773/141.9/30.2</td>
<td>20.0</td>
</tr>
<tr>
<td>II 3.75</td>
<td>3.96</td>
<td>4.74</td>
<td>0.946/0.83</td>
<td>15.53/4.04</td>
<td>1189/173.2/48.4</td>
<td>31.5</td>
</tr>
<tr>
<td>7 Rest</td>
<td>13.41</td>
<td>14.06</td>
<td>16.44</td>
<td>1.046/1.059</td>
<td>4.55/1.13</td>
<td>1044</td>
</tr>
<tr>
<td>I 8.85</td>
<td>9.32</td>
<td>10.67</td>
<td>1.077/1.047</td>
<td>9.67/2.40</td>
<td>1469/203.5/35.1</td>
<td>26.9</td>
</tr>
<tr>
<td>II 6.09</td>
<td>6.37</td>
<td>7.03</td>
<td>1.077/1.005</td>
<td>14.92/3.70</td>
<td>1553/175.1/35.4</td>
<td>30.2</td>
</tr>
<tr>
<td>8 Rest</td>
<td>12.54</td>
<td>13.15</td>
<td>15.50</td>
<td>1.025/0.911</td>
<td>5.63/1.12</td>
<td>1210</td>
</tr>
<tr>
<td>I 7.38</td>
<td>7.81</td>
<td>8.80</td>
<td>1.071/1.054</td>
<td>14.81/2.94</td>
<td>1885/208.0/43.3</td>
<td>37.6</td>
</tr>
<tr>
<td>II 6.85</td>
<td>7.21</td>
<td>8.10</td>
<td>0.989/0.913</td>
<td>16.30/3.23</td>
<td>1919/230.8/49.2</td>
<td>33.6</td>
</tr>
<tr>
<td>9 Rest</td>
<td>12.48</td>
<td>13.08</td>
<td>14.98</td>
<td>1.031/0.951</td>
<td>4.51/1.07</td>
<td>963</td>
</tr>
<tr>
<td>I 8.26</td>
<td>8.60</td>
<td>9.55</td>
<td>1.052/1.006</td>
<td>8.51/2.02</td>
<td>1201/127.1/34.5</td>
<td>29.9</td>
</tr>
<tr>
<td>II 5.36</td>
<td>5.72</td>
<td>6.24</td>
<td>1.005/1.003</td>
<td>14.41/3.42</td>
<td>1343/129.4/39.7</td>
<td>33.6</td>
</tr>
<tr>
<td>10 Rest</td>
<td>13.50</td>
<td>13.96</td>
<td>16.47</td>
<td>0.952/1.033</td>
<td>4.92/0.99</td>
<td>1127</td>
</tr>
<tr>
<td>I 8.55</td>
<td>8.94</td>
<td>9.90</td>
<td>0.956/0.950</td>
<td>9.36/1.88</td>
<td>1370/143.1/40.8</td>
<td>33.1</td>
</tr>
<tr>
<td>II 6.72</td>
<td>7.00</td>
<td>7.70</td>
<td>0.965/0.913</td>
<td>13.02/2.62</td>
<td>1495/145.4/43.3</td>
<td>32.8</td>
</tr>
<tr>
<td>11 Rest</td>
<td>12.19</td>
<td>12.64</td>
<td>14.95</td>
<td>1.021/1.022</td>
<td>4.99/1.21</td>
<td>1036</td>
</tr>
<tr>
<td>I 5.97</td>
<td>6.32</td>
<td>7.09</td>
<td>0.961/1.059</td>
<td>18.46/4.46</td>
<td>1901/228.0/40.0</td>
<td>33.5</td>
</tr>
<tr>
<td>II 4.69</td>
<td>4.92</td>
<td>5.66</td>
<td>1.025/1.104</td>
<td>20.76/5.02</td>
<td>1673/237.6/48.8</td>
<td>31.6</td>
</tr>
</tbody>
</table>

$^{11}$Cr-RBC = $^{11}$Cr-labeled red blood cells, $^{131}$I-Alb = $^{131}$I-labeled albumin, THO = tritiated water, and DCO = carbon monoxide diffusing capacity.
Transit Times and Vascular Volumes.—The change in the mean transit times of the two vascular reference substances, labeled red cells and labeled albumin, with flow is illustrated in Figure 2. In this figure and those that follow, measured values for flows, volumes, or capacities are related to body weight to provide a normalization related to body size. We felt that, for convenient comparison, this procedure would be more practicable than would the use of total lung capacity or surface area. In Figure 2, the mean transit times of the two vascular reference substances, labeled red cells and labeled albumin, decreased with flow, but the decreases did not occur along isovolumic hyperbolic lines. The manner of the declines indicated that the central blood volume increased with the cardiac output.

Figure 3 shows the relation between the transit times of labeled red cells and labeled albumin and the variation in the ratio of labeled albumin transit time to labeled red cell transit time with flow. The regression line relating the two measurements is

\[ \sim t_{\text{Alb}} = 1.030W + 0.184 \quad (r = 0.9997), \]

where \( \sim t_{\text{Mb}} \) and \( t_{\text{RBC}} \) are the mean transit times of the labeled albumin and the labeled red cells, respectively, in seconds.

Values for the central blood volume (CBV) were calculated as the sum of the vascular red cell and plasma spaces, according to the following formula:

\[ \text{CBV} = F_b Hct \bar{t}_{\text{RBC}} + F_b (1 - Hct) - t_{\text{Mo}} \]

where \( F_b \) is the flow of blood in milliliters per second and \( Hct \) is the hematocrit. The central blood volume increased markedly with the cardiac output. The phenomenon is portrayed in the top section of Figure 4. For this illustration, both the central blood volume and the cardiac output were divided by the body weight (BW) in kilograms. The mean regression line through the data, fitted by the method of least squares, is

\[ \text{CBV/BW} = 2.64FJBW + 11.1. \]

The standard error of the estimate about the fitted line is 2.35 ml blood/kg.
The Extravascular Water Space.—The extravascular lung water space (EVLW), in similar fashion, has two components related to the two vascular reference substances (14, 20). If \( f_r \) and \( f_p \) are the fractional volumes of water (ml/ml) in red cells and plasma (0.70 and 0.94, respectively) and if \( t_w \) is the mean transit time for labeled water, then

\[
\text{EVLW} = F_b Hct_f (t_w - t_{RBC}) + F_b (1 - Hct) (t_w - t_{AIO}).
\]

If we define \( f_b \) as the fractional water volume in blood (ml/ml), the expression may be rewritten as:

\[
\text{EVLW} = [F_b Hct_f + F_b (1 - Hct)] t_w
- [F_b Hct_f t_{RBC} + F_b (1 - Hct) t_{AIO}]
= F_b t_w - F_b [Hct (t_w - t_{RBC}) + (1 - Hct) t_{AIO}].
\]

If the final bracketed expression is defined as the composite transit time, \( t_{comp} \), the transit time which water would have if it were carried by bulk flow in the two vascular phases and if it did not leave the vessel, then the expression becomes

\[
\text{EVLW} = F_b f_b (t_w - t_{comp}).
\]

The relation between the transit time difference \( (t_w - t_{comp}) \) and the normalized vascular water flow, \( F_{fs}/BW \), is displayed in Figure 5. The points decrease with flow and appear to conform, at least for the higher cardiac outputs, to an isovolumic hyperbolic line.

The average values for the extravascular lung water and the cardiac output in the three states—rest, first-level exercise, and second-level exercise—are displayed in Table 3. The average cardiac output at first-level exercise was 2.5 times the average at rest; at second-level exercise, it was 3.4 times that value. The average measured extravascular lung water increased by 18% between rest and first-level exercise and then decreased by 4% be-
EXTRAVASCULAR LUNG WATER AND CO DIFFUSING CAPACITY

385

TABLE 3
Average Normalized Values for Cardiac Output, Lung Water, and Single-Breath Carbon Monoxide Diffusing Capacity at Rest, First-Level Exercise, and Second-Level Exercise

<table>
<thead>
<tr>
<th>State</th>
<th>Cardiac output (ml/sec kg⁻¹)</th>
<th>Extravascular water space (g/kg)</th>
<th>Single-breath diffusing capacity (ml/min mm Hg⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>1.06 ± 0.15</td>
<td>2.16 ± 0.47</td>
<td>0.406 ± 0.025</td>
</tr>
<tr>
<td>First-level exercise</td>
<td>2.60 ± 0.78</td>
<td>2.55 ± 0.47</td>
<td>0.519 ± 0.062</td>
</tr>
<tr>
<td>Second-level exercise</td>
<td>3.56 ± 0.67</td>
<td>2.45 ± 0.51</td>
<td>0.588 ± 0.104</td>
</tr>
</tbody>
</table>

All values are means ± SD.

TABLE 4
Variances Associated with Patterns Fitted to the Normalized Measured Extravascular Lung Water Data

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straight line</td>
<td>0.178</td>
</tr>
<tr>
<td>Hyperbola</td>
<td>0.196</td>
</tr>
<tr>
<td>Third-order polynomial which does not pass through the origin</td>
<td>0.162</td>
</tr>
<tr>
<td>Fourth-order polynomial passing through the origin</td>
<td>0.165</td>
</tr>
</tbody>
</table>

between first- and second-level exercise. A paired comparison of the lung water values for each subject was carried out between rest and first-level exercise, and, by use of the t-test, the increase was found to be significant at the P < 0.005 level. However, between first- and second-level exercise, the values were not significantly different even at the 0.30 level. This finding indicates that there is no detectable change in the water space between the first and second levels of exercise.

The values obtained for extravascular lung water, at corresponding values of the cardiac output, are illustrated in the middle section of Figure 4. Both parameters were normalized by dividing by body weight. Extreme values recorded in two individuals bear comment. The lowest recorded value, at rest, was observed in subject 5, the one outstanding athlete of the group. With exercise, a substantial increment in her water space occurred, bringing it into the same general range as that for the other subjects. The two highest values were recorded in subject 11, a young man with an unusual response to the exercise load. At first-level exercise, his cardiac output rose excessively, and he became quite dyspneic and virtually exhausted. Subsequently, only with great encouragement was he able to complete the second exercise period, and during this period there was little further increment in his cardiac output. There were no rales audible at the end of either run. He later noted that he had had frequent extrasystoles during both exercise periods.

We established by the paired comparison test that there was, on the average, a significant increment in the water space values between rest and first-level exercise in our subjects and no significant change between the first and second levels of exercise. Our data, referred to body weight, showed a wide scatter. Previously, we have investigated the changes in measured extravascular lung water with exercise in an animal model, a dog running on a treadmill. These data showed a well-defined increase in lung water in the lower ranges of cardiac output, which was succeeded by a leveling off at higher levels. The data were fitted best by a saturating kind of function, either a rising exponential or a linear hyperbola, but the standard error of the fit was small only when the water space was normalized in relation to the wet lung weight at autopsy. When referred to body weight, the scatter also became relatively large (14, 20). Several patterns have been fitted to the present data by the method of least squares. The variances associated with the fits are displayed in Table 4. The pattern giving the minimum variance, a third-order polynomial that does not pass through the origin, has been superimposed on the data, in the middle section of Figure 4. This fitted function flattens off over the upper range and then begins to increase at the highest levels of cardiac output, where only the data from subject 11 are encountered. The locus fitted is

\[ \text{EVLW/BW} = 1.399 + 1.096 \frac{F_b}{BW} - 0.427 \left( \frac{F_b}{BW} \right)^2 + 0.058 \left( \frac{F_b}{BW} \right)^3. \]

The standard error of the estimate about the curve is 0.40 g water/kg body weight. In view of the abnormal hemodynamic state of subject 11, the terminal increase in the locus may be premature.
The Carbon Monoxide Diffusing Capacity.—The average values for the normalized single-breath carbon monoxide diffusing capacity (DCO\textsubscript{SB}) at the three levels of exercise are listed in Table 3, and the individual values are displayed in the bottom section of Figure 4. A paired t-test was carried out between rest and first-level exercise and between first- and second-level exercise. The differences were significant at the \( P < 0.001 \) and \( P < 0.01 \) levels, respectively. Figure 4 shows that the values increase with increasing flow in an apparently linear fashion. Extrapolation of this linear relation toward zero flow results in a substantial intercept on the ordinate. For the data illustrated in Figure 4, the regression line fitted by the method of the least squares is

\[
\text{DCO}_{\text{SB}}/BW = 0.336 + 0.0698F_{\text{IBW}}.
\]

The steady-state diffusing capacity values are lower than those of the simultaneously measured single-breath diffusing capacity but tend to approach them somewhat more closely at higher values of cardiac output. The proportional change in the relation between these two measured values is illustrated in Figure 6, where the change in the ratio of the single-breath to the steady-state diffusing capacity with increasing cardiac output is displayed. The ratio values slowly decreased toward unity with increased flow.

Discussion

The major unexpected finding in the present study is the apparent discrepancy between the changes observed in the values for extravascular lung water and single-breath carbon monoxide diffusing capacity in the transition from low-level to high-level exercise. On paired comparison, no change was evident in the extravascular lung water, whereas there was a continuous increase in the single-breath carbon monoxide diffusing capacity. Before the inferences of this finding are dealt with, certain other aspects of the study bear examination.

Central Blood Volumes.—From the point of view of the correlative aspects of this study, the most appropriate central volume to measure would have been the pulmonary blood volume. This measurement would have necessitated the placement and the maintenance of pulmonary artery and left atrial catheters in these freely exercising normal subjects. After discussion of this problem by both the investigators and an institutional ethics committee, the opinion was reached that the hazard associated with placement of catheters in these positions and their maintenance in upright exercising normal subjects was larger than could reasonably be undertaken. Instead, superior vena cava-brachial artery central blood volumes were measured. Despite the compromise in experimental design, the data demonstrate a set of remarkable trends. With the recorded approximate tripling of the cardiac output from rest to the higher level of exercise, the measured central blood volume increased by 50%.

One of the unique characteristics of the pulmonary circulation is the large decrease in resistance that occurs with increased flow, a phenomenon attributed in the past to an apparent opening up of new channels with increased flow, without striking changes in pulmonary arterial pressure (21), and more recently to increases in the dimensions of the alveolar (22, 23) and larger vessels. We would then expect the recorded increase in central blood volume. The small decrease in the ventricular components of the central volume, which accompanies steady-state exercise (24), would not be expected to be large enough to mask the increase. The magnitude of the proportional change recorded in the present study, carried out in erect subjects, is larger than expected in terms of past recorded values. However, virtually all previous comparable dilution studies of changes in the central blood volume with exercise have been carried out in the supine position, and the legs have been elevated to pedal the bicycle ergometer. Under these circumstances, the base-line values and the degree of
observed change have been quite different. Assumption of the recumbent position by itself leads to an augmentation of the central blood volume, to an increased base-line value (25). In the present study, the average central blood volume at rest was 1035 ml at an average cardiac output of 4.64 liters/min, and the volume increased at the higher level of exercise by 47% to an average of 1525 ml at a cardiac output of 15.91 liters/min. Braunwald and Kelly (26), studying supine subjects, found an average superior vena cava–brachial artery central blood volume at rest of 1579 ml at an average cardiac output of 6.43 liters/min. The values obtained in the two studies can be compared, since and Kelly (26), studying supine subjects, found an average superior vena cava–brachial artery central blood volume at rest of 1579 ml at an average cardiac output of 6.43 liters/min. The values obtained in the two studies can be compared, since the mean values for the surface areas of the subjects were essentially identical. It should be noted that the mean cardiac output in the supine subjects is 38% higher than that in the erect subjects but that the central blood volume, comparatively, is much larger. It is of the same order of magnitude as that which we found at the higher level of exercise in the erect position. With an exercise-induced increase in cardiac output to 15.02 liters/min, Braunwald and Kelly recorded an increase in the average central blood volume of their supine subjects to 1864 ml, an increment of 18%. Both in an absolute and a comparative sense, the increment is smaller than that which occurred in the erect subjects. More recently, Luepker et al. (27) have developed a method for defining the pulmonary blood volume that involves the separate but simultaneous injection of two different indicators into the pulmonary artery and the left atrium (the latter via a transseptal technique) and the collection of simultaneous dilution curves from the brachial artery. They found that an exercise-induced doubling of the cardiac output in three hemodynamically normal recumbent subjects produced an increment in the pulmonary blood volume of the order expected from the studies of Braunwald and Kelly (26). These studies indicate that a directly measurable increase in the pulmonary component of the central blood volume does indeed occur with exercise.

We conclude that, although the base-line central blood volume is lower in the erect position, there is a greater increment in the volume during exercise than there is in the supine position. The difference reflects the increased effect of the gravitational field on the lungs themselves and on the peripheral venous reservoirs in the erect position and the different pattern of redistribution of blood volume which occurs during exercise as a consequence.

**Dilution Estimates of Extravascular Lung Water.**—The observed values for the extravascular lung water increased from an average of 2.16 g water/kg at rest to 2.55 g water/kg with low-level exercise and then stabilized and became independent of further increases in cardiac output. The values obtained in the present study represent the first systematic examination of the changes that occur in accessible extravascular lung water with exercise in normal man by use of the triple indicator-dilution method (14). In previous examinations of exercising humans (27, 28), a plasma albumin indicator alone has been utilized with tritium-enriched water, and the value used to multiply the transit time difference between the labeled water and the albumin has been the blood flow, so that the value termed an estimated water volume is a misnomer because the apparent units are milliliters of blood and the transit time difference utilized is inappropriate. Alternatively, this same transit time difference has been multiplied by the water flow (29). Neither procedure is correct. Nevertheless, despite the defects in methodology, the measurements in these studies have shown the same trend, a small increase in accessible extravascular lung water with the transition from rest to mild exercise. The apparent leveling off at higher levels of exercise has not previously been observed in human subjects.

The Pulmonary Diffusing Capacity for Carbon Monoxide.—The single-breath pulmonary diffusing capacity for carbon monoxide increased with cardiac output, as expected. Extrapolation of the observed values toward zero flow resulted in a large intercept. This asymptotic behavior was expected, in view of the recording by Burgess et al. (30) of a substantial single-breath carbon monoxide diffusing capacity in a lung in which the pulmonary artery was obstructed so that there was no flow through that vessel. Miller and Johnson (9) have shown that the single-breath carbon monoxide diffusing capacity is dependent on the degree of lung inflation both at rest and during exercise, the observed value being higher at higher alveolar volumes. In our studies, the alveolar volumes utilized for the single-breath determinations, as measured by neon dilution, did not change between rest and the two levels of exercise. Thus, the observed changes in the single-breath diffusing capacity for carbon monoxide were not due to changes in the degree of lung inflation.

The measured values for the steady-state diffusing capacity for carbon monoxide were lower in all cases than were the simultaneously measured values for the single-breath diffusing capacity. The
pattern of increase in the steady-state diffusing capacity with flow was also somewhat different. The initial rest values were quite low (and difficult to measure); the values increased fairly sharply with initial exercise and then tended to level off at higher levels of cardiac output. A hyperbolic relation passing through zero at zero flow has been fitted to steady-state data in the past (7, 31). The different patterns of increase for the single-breath and the steady-state diffusing capacity lead one to expect the ratio of the single-breath measurements to steady-state measurements to be high at low levels of cardiac output and to decrease with exercise. This pattern was observed in the present study.

In steady exercise the body temperature rises, and the increment in temperature itself will result in an increase in the pulmonary diffusing capacity for carbon monoxide (32). The studies of Nielsen and Nielsen (33) indicate that the maximum expected increment in esophageal temperature, at 10 minutes, at our highest level of exercise will be 0.5°C. The study by Powers et al. (32) indicates that this increment in temperature will increase the single-breath diffusing capacity for carbon monoxide by about 2%. This increase is far less than the observed increment, and so the temperature effect must play a minor role in our observations.

The Behavior of the Measured Extravascular Lung Water and the Pulmonary Diffusing Capacity for Carbon Monoxide in the Transition from Low to High Levels of Exercise.—In the transition from rest to low levels of exercise, the measured extravascular lung water increased by an average of 18%. This change could be interpreted to reflect, as we had originally hypothesized, recruitment of additional alveolar sheets. However, in the transition from low to high exercise rates, no further increment in the measured extravascular water space was observed. The inference of these findings is that the perfusion at the low exercise range is already taking place in such a fashion that all parts of the parenchymal tissue are accessible to and are "seen" by the diffusible labeled water indicator, that there is no change in the pattern of distribution of flow paths within the alveolar sheets in the transition from low to high exercise rates, or that, if there is any change, the flow alters in such a fashion that it enters parts of the sheets which have already been accessible to the water label. The latter would imply recruitment of new capillary surface in the absence of recruitment of extravascular space not previously accessible to the water label.

It is now appropriate to examine the possible inferences of these findings for the interpretation of the changes in the pulmonary diffusing capacity with blood flow. It has been traditional to assume that uptake of carbon monoxide from alveolar gas is limited only by the barrier between gas and red cells and that it will increase with blood flow only if the surface subserving gas exchange is increased (12). If we take the lack of change in measurable lung water in the transition from low to high levels of exercise to mean that there is either no increase or a relatively small increase in the alveolar capillary surface available for gas exchange in this transition, then the traditional view proves inadequate. Because of this apparent inadequacy, Goresky and Bach (34) have carried out a model reexamination of the process of carbon monoxide uptake from an alveolus, in which they assumed that the limiting factor in the uptake process is the permeability of the membrane to carbon monoxide and, in addition, that the uptake process in the capillaries is distributed in space, that the capillaries have a finite and defined length. Several new phenomena appear in this modeling corresponding to previously poorly explained experimental observations: (1) the carbon monoxide uptake (the value measured during the determination of the diffusing capacity) increases sharply with flow in a system in which there is no capillary recruitment, (2) the carbon monoxide uptake varies with the initial conditions (the uptake in the single-breath method is expected to be larger than that in the steady-state method), and (3) the maximum rate of uptake of carbon monoxide occurs at flows larger than those usually attained even during maximum exercise.

The system modeled by Goresky and Bach (34), a single rigid capillary, is more restricted than the actual experimental situation. One major difference is that the alveolar sheet is distensible and that the contained blood volume will increase with flow (22, 23) even though the surface will change little.

The potential implications of our experimental findings are thus far-reaching. They lead to the idea that the carbon monoxide diffusing capacity may be in part flow dependent. This interesting concept deserves further exploration to define its applicability.

Acknowledgment

We wish to express our appreciation to Ms. Heather Kennedy and Ms. Denise Joubert for their expert technical assistance and to Ms. Margaret Mulherin for typing this manuscript.

Circulation Research, Vol. 37, September 1975
EXTRAVASCULAR LUNG WATER AND CO DIFFUSING CAPACITY

References

5. BOHR C: Messung der Durch die lungen stattfindenden Gasdiffusion. Skand Arch Physiol 22:261-280, 1909
17. HAMILTON WF, MOORE JW, KINSMAN JM, SPURGILL RG: Simultaneous determination of the greater and lesser circulatory time, of the main velocity of blood flow through the heart and lungs, of the cardiac output, and an approximation to the amount of blood circulating in the heart and lungs. Am J Physiol 184:338-344, 1956
25. SJOSTRAND T: Volume and distribution of blood and their significance in regulating the circulation. Physiol Rev 33:202-228, 1953
Effect of exercise on dilution estimates of extravascular lung water and on the carbon monoxide diffusing capacity in normal adults.
C A Goresky, J W Warnica, J H Burgess and B E Nadeau

doi: 10.1161/01.RES.37.3.379
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/37/3/379

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/