Attenuation of the Ventilatory and Heart Rate Responses to Hypoxia and Hypercapnia with Aging in Normal Men

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ABSTRACT The response of ventilation and of heart rate to hypoxia and hypercapnia was determined in eight young normal men age 22-30 yr and eight elderly men age 64-73. The elderly men were selected and carefully screened to eliminate the possibility of cardiopulmonary disease. All the subjects were born at low altitude and had no significant prior exposure to hypoxia. The ventilatory response to hypoxia was measured as the exponential slope constant, \( k \), of regression lines relating the logarithm of incremental ventilation to \( P_{A0} \) during isocapnic progressive hypoxia. The heart rate response to hypoxia was measured as the percentage change in heart rate between \( P_{A0} = 100 \) and \( P_{A0} = 40 \) mm Hg. The ventilatory response to hypercapnia was measured as the slope of regression lines relating ventilation to \( P_{ACO2} \) during rebreathing with \( P_{ACO2} \geq 200 \) mm Hg. The heart rate response to hypercapnia was measured as the percentage change in heart rate between control values at the start of the rebreathing test and \( P_{ACO2} = 55 \) mm Hg.

The ventilatory and heart rate responses to both hypoxia and hypercapnia were significantly decreased in the elderly men as compared to the young men. Hypoxic ventilatory drive was decreased by 51±6% (mean ±SEM; \( P < 0.001 \)) and hypercapnic drive by 41±7% (\( P < 0.025 \)). The percentage change in heart rate produced by hypoxia was 34±5% (mean ±SEM) in the young normals and 12±2% in the old normals (\( P < 0.005 \)). Similar figures for heart rate in response to hypercapnia were 15±3% and -1±1% for the young and old normal groups (\( P < 0.001 \)).

We conclude that ventilatory and heart rate responses to hypoxia and hypercapnia diminish with age. These alterations in both ventilatory and circulatory controls could make older individuals more vulnerable to hypoxic disease states.

INTRODUCTION

Within a group of normal subjects, there may be considerable variation in the ventilatory response to hypoxia and hypercapnia (1, 2). The reasons for this variation are unclear, but two important factors that appear to reduce the ventilatory response to hypercapnia and greatly diminish or abolish the response to hypoxia, are prolonged exposure to hypoxia (3) and athletic physical conditioning (4). This report will present evidence that a third factor, increasing age, can also attenuate hypoxic and hypercapnic ventilatory drive.

METHODS

Subjects. The old normal subjects were selected volunteers from a larger group of elderly normal men participating in a long term epidemiological study on heart disease (5). In connection with this epidemiological study, they have been followed with periodic history questionnaires, physical examinations, chest X rays, electrocardiograms, and the pulmonary function tests listed in Table I. None of the old normal subjects had ever smoked cigarettes. Criteria for subject selection were no evidence for heart disease or cerebrovascular disease and birth at or near sea level with no previous sojourns at high altitude for over 2 mo in any 1 yr. Thus the old normal men in this study constitute a select subject group free of significant heart, lung, and vascular disease and with no significant prior exposure to hypoxia.

The young normal control subjects were male college students who had no previous experience with respiratory studies, who had not spent over 2 mo at high altitude, and who were not using drugs. Hypoxic ventilatory response data on the control subjects has been previously reported (6).

Hypoxic response. A detailed description of the method used in these studies has been reported elsewhere (6). The subject breathed through a respiratory valve (Lloyd) into a circle with a variable CO\(_2\) absorber bypass rebreathing system. CO\(_2\) was continuously sampled by an infrared CO\(_2\) analyzer (Beckman LB-1; Beckman Instruments, Inc., Fullerton, Calif.). End-tidal O\(_2\) was automatically sampled from beyond the inspiratory valve using the method described by Severinghaus and Hamilton (10). Differences between alveolar PO\(_2\) obtained by this method and arterial PO\(_2\) were less than 4 mm Hg when \( P_{A0} = 40 \) mm Hg in the young

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normal subjects. Arterial blood samples were not obtained from the old normal men. Various gas mixtures (N₂, O₂, CO₂) were added via flow meters to ports in the circuit for control of desired gas tensions. A suction flow meter permitted this addition of gases without changing the volume of the system. Heart rate was recorded from ECG electrodes applied to the chest. Ventilation was transduced by a potentiometer coupled to a 13.5 l spirometer (Warren E. Collins, Inc., Braintree, Mass.) within the circle-breathing system. All variables were recorded on a polygraph recorder (Grass Model 7, Grass Instrument Co., Quincy, Mass., or a Gilson MSP, Gilson Medical Electronics, Inc., Middleton, Wisc.). Alveolar P₀₂ was held at 120 mm Hg for 2 min before beginning the hypoxic response tests in order to determine each subject's resting Pₐₚₒ₂. Pₐₚₒ₂ was then lowered from 120 to 40 mm Hg over a period of 4-5 min. The induction of hypoxia in this study was somewhat more rapid than that employed by other investigators (11). We have found that there is no difference in results obtained by this method and slower ones (6). Byrne-Quinn, Sodal, and Weil, using the same isocapnic progressive hypoxia technique but a different method of data analysis, also found no difference in results when lowering Pₐₚₒ₂ over 5 min as compared with 15 min (12). With practice, the variable CO₂ absorber bypass could be adjusted to hold Pₐₚₒ₂ within 1 mm Hg of the previously determined resting level. It was occasionally necessary to add CO₂ to the circuit to achieve this degree of Pₐₚₒ₂ control. Two isocapnic hypoxic response tests were done in each subject with an intervening rest period.

Ventilation in the hypoxic response tests was measured by averaging inspiratory volume over a minimum of five breaths at approximately each 10 mm Hg fall in Pₐₚₒ₂. The relationship of ventilation to P₀₂ at a constant Pₐₚₒ₂ has been described as hyperbolic (11). Previously reported work using this technique, however, demonstrated that the logarithm of incremental ventilation is approximately a linear function of P₀₂ (6). Incremental ventilation is determined by subtracting from all ventilation measurements their non-hypoxic component. The figure used to represent this non-hypoxic component was 85% of the ventilation at Pₐₚₒ₂ = 100 mm Hg. This constant is based on calculations made by Severinghaus, Bainton, and Carrellas in high altitude natives showing that about 15% of the resting ventilatory drive at P₀₂ = 100 mm Hg is provided by the peripheral chemoreceptors (13). This figure was confirmed by Wade, Lar son, Hickey, Ehrenfeld, and Severinghaus in a study of patients with denervated peripheral chemoreceptors (14). Using this method of analysis, the relationship between ventilation and P₀₂ at constant Pₐₚₒ₂ can be expressed by the equation

\[ \Delta V_i = \Delta V_e \left[ \frac{P_0}{273} \right] \]

where \( \Delta V_e \) is the ventilation intercept at P₀₂ = 0 and \( k \) is the decrement in P₀₂ required to increase ventilation by a factor of e(2.718). Thus a small value for \( k \) indicates a large hypoxic ventilatory drive. Constants for the equation were determined by the linear regression of ln (V_i - 0.85 V_min) on P₀₂. At least 12 points were used in each regression. These data were added via flow meters to ports in the circuit to determine 

\[ \text{Regression analysis.} \]

**TABLE I**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Vital capacity</th>
<th>Total lung capacity*</th>
<th>FVC</th>
<th>FEV₁0. *</th>
<th>FEV₁0.5/FVC</th>
<th>D₁co₂SB</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. C.</td>
<td>4.549</td>
<td>7.520</td>
<td>3.000</td>
<td>0.69</td>
<td>0.24</td>
<td>0.19</td>
</tr>
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<td>A. N.</td>
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<td>6.786</td>
<td>3.275</td>
<td>0.75</td>
<td>0.24</td>
<td>0.19</td>
</tr>
<tr>
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<td>6.334</td>
<td>2.800</td>
<td>0.75</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
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<td>3.651</td>
<td>5.831</td>
<td>2.175</td>
<td>0.68</td>
<td>0.17</td>
<td>0.15</td>
</tr>
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<td>2.150</td>
<td>0.71</td>
<td>0.17</td>
<td>0.15</td>
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<tr>
<td>L. M. C.</td>
<td>4.867</td>
<td>7.540</td>
<td>2.825</td>
<td>0.66</td>
<td>0.28</td>
<td>0.26</td>
</tr>
<tr>
<td>J. H.</td>
<td>4.619</td>
<td>7.952</td>
<td>2.750</td>
<td>0.57</td>
<td>0.20</td>
<td>0.18</td>
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<td>1.950</td>
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<td>0.17</td>
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<td>6.551</td>
<td>2.616</td>
<td>0.71</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>±SSEM</td>
<td>276</td>
<td>415</td>
<td>165</td>
<td>3</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁0.₅, forced expiratory volume in 1.0 s; FVC, forced vital capacity; D₁co₂SB, single breath carbon monoxide diffusing capacity.

* Total lung capacity was calculated from functional residual capacity measured by open circuit N₂ washout.

† Numbers in parenthesis indicate percent of predicted value obtained from references 7-9.

Heart rate in the hypoxic response test was measured by comparing actual rates and percentage change between control heart rates at P₀₂ = 100 mm Hg and heart rates at P₀₂ = 40 mm Hg.

**CO₂ response.** The ventilatory response to hypercapnia was determined by the rebreathing method described by Read (16). A 6 liter bag in a bottle was arranged so that the subject could rebreathe from the main circuit or back in forth into the bag. The rebreathing bag was prefilled with 5% CO₂ in O₂. Each subject rebreathed from the bag for 4 min or until Pₐₚₒ₂ = 65 mm Hg. Two rebreathing tests were done with an intervening rest period. Pₐₚₒ₂ remained over 200 mm Hg throughout the rebreathing period. Ventilation in the hypercapnic response test was measured by averaging inspiratory volume over 30-s intervals after discarding the first 30 s of the test. Thus approximately 14 points were obtained for analysis on each subject. The relationship relating ventilation to Pₐₚₒ₂ is \( V_i = S(Pₐₚₒ₂ - B) \) where \( B \) is the extrapolated Pₐₚₒ₂ at \( V_i = 0 \) (intercept on the abscessa or Pₐₚₒ₂ axis) and \( S \) is the slope of the CO₂ response line (liter/min × mm Hg⁻¹) (17). Constants for this equation were obtained by the linear regression of \( V_i \) on Pₐₚₒ₂.

Analysis of the heart rate response to hypercapnia was identical to that done for hypoxia. Percentage change and actual rate differences were calculated between control heart rates immediately after the start of rebreathing and heart rates at Pₐₚₒ₂ = 55 mm Hg.

Group comparisons for all of the data were made with an unpaired \( t \) test.

**Attenuation of Chemoreceptor Function with Age**
TABLE II
Ventilatory Response to Hypoxia and Hypercapnia in Young and Old Normal Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Ht</th>
<th>Wt</th>
<th>PAO2</th>
<th>ΔV̇₂O₂</th>
<th>ΔV̇₁₀₀</th>
<th>k</th>
<th>S</th>
<th>B</th>
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</tr>
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<td>22</td>
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<td>63.5</td>
<td>42</td>
<td>35.0</td>
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<td>27.1</td>
<td>4.2</td>
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<td>45.7</td>
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<td>3</td>
<td>30</td>
<td>188</td>
<td>85.0</td>
<td>43</td>
<td>45.2</td>
<td>0.8</td>
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<td>41.0</td>
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<tr>
<td>4</td>
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<td>65.5</td>
<td>40</td>
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<td>0.7</td>
<td>17.1</td>
<td>2.5</td>
<td>44.8</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
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<td>64.5</td>
<td>40</td>
<td>35.1</td>
<td>8.5</td>
<td>29.6</td>
<td>2.1</td>
<td>37.5</td>
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<tr>
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<td>3.9</td>
<td>34.0</td>
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<td>42.0</td>
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<tr>
<td>7</td>
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<td>173</td>
<td>59.0</td>
<td>40</td>
<td>45.7</td>
<td>7.5</td>
<td>33.2</td>
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<td>42.7</td>
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<tr>
<td>8</td>
<td>28</td>
<td>176</td>
<td>65.5</td>
<td>40</td>
<td>65.3</td>
<td>3.4</td>
<td>20.5</td>
<td>6.3</td>
<td>41.9</td>
</tr>
<tr>
<td>Mean</td>
<td>25.6</td>
<td>179.3</td>
<td>69.9</td>
<td>40.9</td>
<td>40.1</td>
<td>3.8</td>
<td>24.5</td>
<td>3.4</td>
<td>43.0</td>
</tr>
<tr>
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<td>3.2</td>
<td>0.9</td>
<td>4.7</td>
<td>1.0</td>
<td>2.6</td>
<td>0.5</td>
<td>1.2</td>
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<tr>
<td>Old normals</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>H. C.</td>
<td>73</td>
<td>182</td>
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<td>41</td>
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<td>72.7</td>
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<td>44.7</td>
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<tr>
<td>A. N.</td>
<td>68</td>
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<td>73.8</td>
<td>40</td>
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<td>2.7</td>
<td>36.3</td>
<td>1.5</td>
<td>43.4</td>
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<tr>
<td>L. C.</td>
<td>70</td>
<td>175</td>
<td>91.0</td>
<td>42</td>
<td>7.6</td>
<td>2.6</td>
<td>53.5</td>
<td>1.2</td>
<td>39.0</td>
</tr>
<tr>
<td>W. K.</td>
<td>70</td>
<td>175</td>
<td>85.0</td>
<td>37</td>
<td>7.3</td>
<td>2.6</td>
<td>57.4</td>
<td>3.1</td>
<td>46.2</td>
</tr>
<tr>
<td>E. M.</td>
<td>64</td>
<td>179</td>
<td>92.0</td>
<td>41</td>
<td>9.6</td>
<td>2.0</td>
<td>32.3</td>
<td>2.6</td>
<td>45.5</td>
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<td>179</td>
<td>84.0</td>
<td>37</td>
<td>16.7</td>
<td>2.3</td>
<td>30.7</td>
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<td>42.4</td>
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<tr>
<td>J. H.</td>
<td>71</td>
<td>178</td>
<td>72.6</td>
<td>39</td>
<td>10.3</td>
<td>2.4</td>
<td>52.5</td>
<td>1.9</td>
<td>46.0</td>
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<tr>
<td>W. L.</td>
<td>72</td>
<td>170</td>
<td>78.0</td>
<td>38</td>
<td>8.5</td>
<td>3.3</td>
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<tr>
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<td>69.6</td>
<td>176.9</td>
<td>82.6</td>
<td>39.4</td>
<td>10.2</td>
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<td>49.7</td>
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<td>43.8</td>
</tr>
<tr>
<td>SEM</td>
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<td>1.2</td>
<td>2.6</td>
<td>0.7</td>
<td>1.2</td>
<td>0.2</td>
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<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.025</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RESULTS

The ventilatory response to hypoxia at constant CO₂ for each of the young and old normal subjects is summarized in Table II. Average response curves for both subject groups are shown in Fig. 1, detailed results of two isocapnic response tests in one of the old men are shown in Fig. 2, and individual responses are shown in their exponential form in Fig. 3. Although control ventilations (ΔV₁₀₀) were more variable in the young normal subjects, there was no significant difference in ΔV₁₀₀ between the two groups. The ventilatory response to hypoxia was strikingly diminished in the old normal subjects. The decrement in PAO₂ required to increase ventilation by a factor of e(2.718), k, was 49.7±5.4 mm Hg (mean±SEM) in the old normal subjects and 24.5±2.6 mm Hg in the young normal men. This difference was highly significant (P<0.001). Similarly the incremental ventilation at PAO₂=40 mm Hg, ΔV₁₀₀, was 40.1±4.7 liters/min (mean±SEM) in the young normal men and 10.2±1.2 liters/min in the old normal men, also a highly significant difference (P<0.001). The slopes of the individual response lines relating in ΔV₁ to PAO₂ in the old normal subjects are not as steep as those of the young normals (Fig. 3). In addition, ΔV₁ at PAO₂=40 is uniformly smaller in the old normal group without any overlap between groups.

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Figure 2  Ventilatory response to progressive hypoxia in subject L. M. C. showing analysis of ventilation as an exponential function of \( P_{O_2} \). Individual data points from two separate tests are plotted in the left-hand panel and replotted on a semilog scale after subtracting \( 0.85 \times \text{ventilation at } P_{A02} = 100 \text{ mm Hg} \) in the right hand panel. The solid line was calculated by linear regression analysis. \( P_{A02} \) was constant at 37 mm Hg.

The ventilatory response to hypercapnia in each subject is shown in Table II and Fig. 4. There was no difference in the \( P_{A02} \) at \( V_I = 0 \) liter/min, \( B \), in the two groups. The slope of the response lines relating \( V_I \) to \( P_{A02} \) was \( 3.4 \pm 0.5 \) liters/min \( \times \) mm Hg\(^{-1} \) (mean \( \pm \text{SEM} \)) in the young normal subjects and 2.0 \( \pm 0.2 \) liters/min \( \times \) mm Hg\(^{-1} \) in the old normal men. This difference was significant \( (P < 0.025) \) but not as great as the difference between the two groups in hypoxic ventilatory drive. This is further illustrated in Fig. 4 where some overlap in the CO\(_2\) response lines can be seen between the young and old normal subjects.

Figure 3  Ventilatory response to progressive hypoxia in each of the young (broken lines) and old (solid lines) normal men. \( P_{A02} \) is constant at each subject's resting level. \( \Delta V_I = V_I - 0.85 \times \text{ventilation at } P_{A02} > 200 \text{ mm Hg} \). Individual subjects are represented by the following symbols: 1 and H. C., \( \bullet \); 2 and A. N., \( \times \); 3 and L. C., \( \Delta \); 4 and W. K., \( \bigcirc \); 5 and E. M., \( \square \); 6 and L. M. C., \( \triangle \); 7 and J. H., \( \blacksquare \); 8 and W. L., \( \varnothing \).

Figure 4  Ventilatory response to rebreathing CO\(_2\) (\( P_{A02} > 200 \text{ mm Hg} \)) in each of the young (broken lines) and old (solid lines) normal subjects. Symbols for individual subjects are the same as in Fig. 1.

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The heart rate response to hypoxia and hypercapnia is shown in Table III. In both instances the control heart rates were significantly higher (P < 0.005 for hypoxia and <0.025 for hypercapnia) in the young normal subjects. Hypoxia (P$_{AO_2}$ = 40 mm Hg) produced a heart rate of 132±8/min (mean ±SEM) in the young normal men and 87±4/min in the old normal subjects, a highly significant difference (P < 0.001). The percentage increase in heart rate due to hypoxia was 34±5% in the young normals and 12±2% in the old normals (P < 0.001). The percentage increase in heart rate between control at the start of the rebreathing test and P$_{AO_2}$ = 55 mm Hg was 15±3% (mean ±SEM) in the young normal men. In contrast to this modest increase in the young normals, hypercapnia produced no change in the heart rate of the old normal men. In fact the average response was a decrease of 1±1% (mean ±SEM) in the old normal group. The difference between groups both in actual rate and percentage change due to hypercapnia were highly significant (P < 0.005 for actual rate and P < 0.001 for percentage change).

**DISCUSSION**

The data presented in this study indicate that hypoxic and hypercapnic ventilatory drive diminishes with increasing age. Since this observation is new, it is necessary to consider the possibility that it was produced artifactually by the testing methods, data analysis, or subject selection.

The use of progressive hypoxia at constant P$_{CO_2}$ as a technique for determining the ventilatory response to hypoxia was described by Loeschcke and Gertz (18). More recently, Weil et al. used a slightly longer version of this technique than that used in this study in 10 young normal men (11). They calculated an average ΔVw in this group of 17.0±1.5 (mean ±SEM) liters/min × m$^{-2}$ BTPS, a value very similar to the 21.5±2.7 liters/min × m$^{-2}$ in our young normal subjects. (Note the correction for body surface area.) Several methods for analyzing the relationship between ventilation and P$_{O_2}$ are described in the literature. These include the hyperbolic shape parameter of Weil et al. (11) and the ΔVw index of Severinghaus et al. (13). Calculation of the ventilatory response to hypoxia in our subjects using either of these indices does not alter the difference between the young and old normal groups. The high oxygen rebreathing CO$_2$ response test is a well accepted technique used both in normal subjects (16) and patients (19). The average slope in our young normal men of 3.4±0.5,
Attenuation of Chemoreceptor Function with Age

(mean ±SEM) compares closely with that obtained by Read of 2.7±0.3 in 21 normal subjects of unspecified age (16). Recently Patrick and Howard found that the slope of the line relating ventilation to tidal volume during hyperoxic rebreathing CO₂ response was inversely related to age (20). The slope of the response line relating ventilation to P_{A\text{CO}_2} was also decreased in their older as compared with their younger subjects, but the difference was not significant. Further comparison between this study and ours is difficult because their older subjects were only 44±5 yr (mean ±SD). Although no information is available on how transient tests of hypoxic and hypercapnic ventilatory response compare with steady-state methods in older subjects, it appears unlikely that testing methods or analytical techniques can account for the response differences in young and old subject groups. Since arterial blood samples were not obtained in the old normal men, it is not possible to quantitate the exact humoral stimulus to the chemoreceptors in the two subject groups. Mellengaard (21) and Raine and Bishop (22) found that alveolar to arterial oxygen difference increased with age. Since all the subjects were exposed to an alveolar PaO₂ of 40 mm Hg, it is likely that the old normal men received a greater humoral stimulus than the young men during the hypoxic response tests and that our data actually underestimate the extent that hypoxic ventilatory drive diminishes with age.

There remains the possibility that other factors unrelated to chemoreceptor function were operating in the old normal subjects. Several alterations in pulmonary mechanics are known to occur with increasing age. Among these changes are loss of elastic recoil and a decrease in vital capacity with an increase in residual volume and no change in total lung capacity (23-25). Brodovsky, MacDonell, and Cherniack (26) and Milic-Emili and Tyler (27) have found that mechanical work is a more accurate gauge of the respiratory response to CO₂ than ventilation. Although alterations in mechanical lung function may account for some of the diminished ventilatory response to hypoxia and CO₂ seen in the old normal men, it seems unlikely that they can entirely explain their marked attenuation in chemoreceptor function. The old normal subject group was carefully screened to be free of detectable heart and lung disease. In addition, the maximum ventilations reached by the old normal subjects are generally considerably less than their expected maximum breathing capacity calculated by multiplying their FEV₁×30 (28). Thus the conclusion remains that age in some way directly attenuates chemoreceptor function.

Although there are isolated normal individuals with no ventilatory response to hypoxia (1, 6), the only conditions previously reported to be associated with attenuation of chemoreceptor function are hypoxia from birth (29-32), prolonged exposure to hypoxia in adulthood, (3, 33) and athletic physical conditioning (4). Byrne-Quinn, Weil, Sodal, Fillen, and Grover found that hypoxic ventilatory drive was reduced by 65% and hypercapnic drive by 53% in 13 athletes studied at rest as compared with non-athlete controls (4). Weil, Byrne-Quinn, Sodal, Fillen, and Grover found comparable reductions of 57% for hypoxic drive and 35% for hypercapnic drive in 10 long-term non-native residents of Leadville, Colo. (3,100 m) when compared with natives of Denver, Colo. (1,600 m) (3). Hypoxic ventilatory drive was reduced by an average of 51% and hypercapnic drive by an average of 41% in the old normal men of this study. The pattern of attenuation of chemoreceptor function is reasonably similar in all three of these situations and suggests the possibility that some of the factors responsible for the loss of hypoxic and hypercapnic ventilatory drive lie within the peripheral chemoreceptors themselves or in the integrating pathways for the peripheral chemoreceptor impulses within the central nervous system. This premise is based on the assumption that the peripheral chemoreceptors account for about half of the hypercapnic drive in man (34), and the findings of Sørensen and Cruz (35) and Lefrancois et al. (36) that high altitude natives have a decreased response to rapid step increases in CO₂. Although the precise defect in the pathway of the peripheral chemoreceptor impulses cannot be determined by this or the other studies cited, it is apparent that virtually all of the peripheral chemoreceptor contribution to hypercapnic ventilatory drive is lost while considerable hypoxic ventilatory drive is retained. This implies either a highly selective effect of age on the peripheral chemoreceptors or, more likely, that alterations in peripheral chemoreceptor function may be one of multiple factors responsible for diminished hypoxic and hypercapnic ventilatory drive in our old normal subjects.

Wade et al. found that hypoxia at constant P_{A\text{CO}_2} increased systolic blood pressure before and decreased it after bilateral carotid body denervation in four patients undergoing bilateral carotid endarterectomy (14). These findings were later confirmed by Lugliani, Whipp, and Wasserman in eight asthmatics with bilateral carotid body resection (37). Lugliani et al. also found that the tachycardia of hypoxia was not affected by carotid body resection. Both Wade et al. (14) and Lugliani, Whipp, Seard, and Wasserman (38) report intact baroreceptor function after chemoreceptor denervation in their subjects. It is possible that the diminished heart rate response to hypoxia in the old normal men indicates a loss of both baroreceptor and chemoreceptor function with age.

The precise mechanism for the attenuation of the ventilatory and heart rate response to hypoxia and hyper-
capnia with aging cannot be elicited from this study. It is likely that multiple factors such as chemoreceptor function, baroreceptor function, and possibly the sympathetic nervous system may all play a role. Regardless of the mechanism involved, the finding that the ventilatory and heart rate responses to hypoxia and hypercapnia diminish with increasing age is of considerable clinical importance. First, it exposes one more variable that must be considered in the regulation of respiration in patients or normal individuals particularly if they are also exposed to chronic hypoxia. Secondly, it suggests that the process of aging is associated with the loss of this potentially important protective mechanism. Thus, the patient population most often exposed to hypoxic disease states is also least able to respond to this threat. Further, the usual diagnostic clues indicating the onset of hypoxia may be absent. Hypoxia in the elderly patient might not be signaled by either respiratory distress or tachycardia.

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