Nonlinear increases in diffusing capacity during exercise by seated and supine subjects

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STOKES, DAVID L., NEIL R. MACINTYRE, AND JAY A. NADEL. Nonlinear increases in diffusing capacity during exercise by seated and supine subjects. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 51(4): 858-863, 1981.—To study the effects of exercise on pulmonary diffusing capacity, we measured the lungs' diffusing capacity for carbon monoxide (DLCO) during exhalation from 30 to 45% exhaled vital capacity in eight healthy subjects at rest and during exercise while both sitting and supine. We found that DLCO at these lung volumes in resting subjects was 26.3 ± 3.2% (mean ± SE) higher in the supine than in the sitting position (P < 0.001). We also found that, in both positions, DLCO at these lung volumes increased significantly (P < 0.001) with increasing exercise and approached similar values at maximal exercise. The pattern of increase in DLCO with an increase in oxygen consumption in both positions was curvilinear in that the rate of increase in DLCO during mild exercise was greater than the rate of increase in DLCO during heavy exercise (P = 0.02). Furthermore, in the supine position during exercise, it appeared that DLCO reached a physiological maximum.

pulmonary capillary blood volume, exercise; carbon monoxide, gravity

THE PULMONARY CAPILLARY NETWORK is a passive vascular bed whose volume is determined by the compliance of the capillaries and the balance between distending pressures and perivascular pressures (5). The compliance of this capillary bed is quite high (7); so small changes in distending pressure cause large changes in volume. Specifically, the small increases in pulmonary vascular pressures that accompany exercise will elicit substantial increases in pulmonary capillary blood volume.

Changes in pulmonary capillary blood volume are thought to be reflected by changes in the lungs' diffusing capacity for carbon monoxide (DLCO) (20, 32, 35). Indeed, many people have studied DLCO in an attempt to describe the behavior of the pulmonary capillary bed during exercise. However, no consensus has developed about the magnitude or the pattern of the observed increases in DLCO from rest to maximum exercise. Some investigators report finding a curvilinear increase in DLCO during exercise with a greater rate of increase at low work rates than at high work rates (4, 8, 9, 14, 29). Others, however, report linear increases even during maximum exercise (6, 15, 16). This controversy may in part be due to difficulties in measuring DLCO during exercise. Steady-state measurements of DLCO can be affected by hyperventilation alone (1, 31), exercise-induced changes in ventilation-perfusion relationships (26), and exercise-induced changes in the lung volume at which carbon monoxide uptake is measured (24). Additionally, the steady-state technique requires more inhaled carbon monoxide than other techniques; thus consideration of carbon monoxide backpressure may become important after repeated measurements. Single-breath measurements of DLCO are even more difficult to obtain accurately during exercise. Breath holding at high work rates is difficult, and subjects may inadvertently perform Müller maneuvers under these conditions. Additionally, hypoxemia during breath holding at high work rates, as well as changes during exercise in inspiratory and expiratory flow rates (thus affecting timing estimates), may affect the single-breath measurement of DLCO during exercise (13, 18).

To shed light on this controversy, we did experiments using the continuous-exhalation technique for measuring DLCO (28). This technique uses a rapidly responding carbon monoxide analyzer to measure carbon monoxide concentrations continuously throughout a slow exhalation. Unlike the single-breath, steady-state, or rebreathing technique, a single overall lung DLCO is not obtained by this technique. Rather, DLCO is calculated multiple times over small intervals of the exhalation. A single value for DLCO, which can be compared at rest and exercise in various positions, however, can be obtained by calculating a mean DLCO from all of the DLCO's measured from 30 to 45% of exhaled vital capacity. This can be done because DLCO measured at lung volumes from 30 to 45% of exhaled vital capacity in normal subjects is relatively constant (28). In preliminary studies on normal subjects, we have found this measurement to be a convenient and reproducible way to express lung diffusing capacity under various conditions of exercise and position.

This technique appears to offer several advantages over other techniques of measuring DLCO during exercise. First, it requires only a single inhalation of carbon monoxide for each measurement, and the respiratory maneuver is easy to perform, even at high work rates. Second, the technique is unaffected by exercise ventilatory patterns. Third, because DLCO is measured over the same range of lung volumes during each test, inspired and expired volumes need not be identical for each measurement. Fourth, in comparison with the single-breath technique, this technique measures carbon monoxide concent-
trations directly over precise time intervals, thereby eliminating assumptions regarding timing intervals and initial gas dilution. Like other techniques, however, DLCO measured in this way can be affected by Müller or Valsalva maneuvers as well as by hypoxemia produced during the test. Additionally, this technique has unique assumptions and potential errors of its own. We make important assumptions regarding the meaning of carbon monoxide uptake as measured during changing lung volumes and regarding the behavior of regional lung emptying patterns with changes in exercise and position.

In spite of these potential problems with the technique, we felt that this unique way of measuring carbon monoxide uptake might offer insight into the behavior of pulmonary diffusing capacity under exercise conditions in different positions. Accordingly, we used this technique to measure DLCO in eight normal subjects at rest and during incremental exercise in both the sitting and the supine positions.

METHODS

The subjects were eight fully informed, healthy adults (7 men and 1 woman, 19–29 yr old; Table 1). Results for screening tests of pulmonary function, performed as described previously (10), were normal in each subject.

Each subject participated in one study session per day. A study session consisted of a resting period followed by exercise at three increasing work rates in either the sitting or the supine position. Each subject completed at least one study session in both the sitting and the supine positions. 5 of the subjects exercised on 4 separate days (2 days in the sitting position, 2 days in the supine position) and the results from both days were combined. During each session, we measured minute volume of ventilation, oxygen consumption, heart rate, and DLCO at rest and during exercise after ventilation became steady (generally after 3–4 min at a given work rate).

Ventilation was measured with a Tissot spirometer, and exhaled concentrations of oxygen, carbon dioxide, and nitrogen were analyzed by a mass spectrometer (Perkin-Elmer MGA-1100).

Diffusing capacity was determined by the continuous-exhalation technique (28). For this technique, the subject inhaled the test gas (0.3% CO-10% He-21% O2-66% N2) from residual volume to total lung capacity and then exhaled slowly (0.5 l/s with a mouth pressure of 5 cmH2O) to residual volume. A rapidly responding infrared analyzer (Andros Corp., Berkeley, CA) measured carbon monoxide concentration, and the mass spectrometer measured helium and oxygen concentrations. Flow into and out of a bag-in-box was measured by a pneumotachograph (Fleisch no. 3) connected to a differential pressure gauge (Validyne DP-45). An on-line computer (PDP 11/34) monitored the gas concentrations and integrated flow to obtain inhaled and exhaled volume. The computer, calculated total lung capacity by multiplying the inhaled vital capacity by the helium dilution after 50% of the vital capacity was exhaled. The exhaled vital capacity was then divided into overlapping 10% intervals separated by 2% decrements in the vital capacity.

The lung volume within each 10% interval was calculated as a weighted average (28)

$$V = \frac{(V_{\text{beg}} - V_{\text{end}})}{\ln(1 + [V_{\text{beg}} - V_{\text{end}}]/V_{\text{beg}})}$$

where $V$ is lung volume, $V_{\text{beg}}$ is lung volume at the beginning of the interval, and $V_{\text{end}}$ is lung volume at the end of the interval. The first 10% of the exhaled vital capacity was discarded as dead space. Measured carbon monoxide concentrations with respect to helium (to correct for sequential emptying of different lung regions) were then used in the Krogh equation to calculated DLCO over subsequent 10% intervals of the vital capacity.

$$DLCO = (60 \frac{V}{[Pt - 47]t} \ln([CO]/[He])/[CO]/[He])$$

where $V$ is lung volume, $P_t$ is barometric pressure, $t$ is time, and $[CO]/[He]$ and $[CO]/[He]$ are carbon monoxide concentrations, with respect to helium, at the beginning and end of each 10% decrement of vital capacity. This process was repeated at 2 intervals of the exhaled vital capacity such that 40 values for DLCO were obtained (from 10 to 90% exhaled vital capacity). The 40 values of $DLCO$ were then plotted against lung volume for a single exhalation. A single value for DLCO, which could be compared at various levels of exercise in various positions, was calculated as a mean of the values of DLCO obtained between 30 and 45% of exhaled vital capacity (Fig. 1).

To normalize the data for all eight subjects, we expressed individual DLCO's as a percent of predicted resting single-breath DLCO (10) and oxygen consumption as a percent of predicted maximal oxygen consumption (17).

To compare mean values of DLCO measured in subjects in the sitting and supine positions at rest and at maximal exercise, we used a two-way analysis of variance and a Newman-Keuls multiple range test. To determine how DLCO increased during exercise, we measured the increase in DLCO per increase in oxygen consumption during the initial work rates (up to 50% of maximal oxygen consumption) and the increase in DLCO per increase in oxygen consumption during the subsequent heavier work rates (as measured by a least-squares linear regression). These rates of increase in the sitting and supine positions.

### Table 1. Physical and cardiovascular variables in seated subjects

<table>
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<tr>
<th>Subj No</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Ht, cm</th>
<th>Weight, kg</th>
<th>TLC, liters</th>
<th>DLCO, ml/min·torr</th>
<th>HR, beats/min</th>
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</tr>
<tr>
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<td>M</td>
<td>25</td>
<td>180</td>
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</tr>
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<tr>
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TLC, total lung capacity; DLCO, lung's diffusing capacity for carbon monoxide measured from 30 to 45% of exhaled vital capacity while subjects were resting in the sitting position; HR, heart rate during maximal exercise.
were then compared by the Wilcoxon sign-rank test. Additionally, the rates of increase during the heavier work rates were compared by an analysis of covariance.

RESULTS

In the sitting position, DLCO increased during exercise in a curvilinear fashion as oxygen consumption increased (i.e., DLCO increased more during mild exercise than during heavy exercise; $P = 0.02$). In the supine position, DLCO at rest was significantly higher than DLCO at rest in the sitting position ($P < 0.001$). Diffusing capacity in the supine position also increased during exercise in a curvilinear fashion as oxygen consumption increased (i.e., DLCO again increased more during mild exercise than during heavy exercise; $P = 0.02$). These patterns of increase occurred in every subject (Fig. 2) and are reflected in the normalized mean data (Fig. 3). Although a similar maximum DLCO is approached during maximal exercise in both positions, it appears that in the supine position this physiological maximum may be approached during moderate work rates and then remain relatively constant through subsequent work rates (i.e., the slope of the increase in DLCO with increasing oxygen consumption during moderate and heavy exercise in the supine position is not significantly different from zero for the group as a whole). In our one female subject (subj 8), who was small in stature and had a small total lung capacity, the absolute increase in DLCO was less during exercise than that observed in the other subjects. However, the pattern of increase (i.e., a more rapid increase in DLCO at low levels of exercise as compared with high
DIFFUSING levels of exercise) was similar to the pattern observed in the other subjects.

DISCUSSION

To interpret our results, the unique features and assumptions of our technique need to be considered. This technique measures carbon monoxide uptake directly over measured time intervals and at various lung volumes. It thus offers us the opportunity to measure DL\textsubscript{CO} in a new way at many different lung volumes. This technique, however, has several potential sources of error. First, we assume that carbon monoxide uptake, when measured over 10% decrements in vital capacity, can be expressed as a single exponential that is reflective of the mean alveolar volume during the measurement. Furthermore, we assume that the effects of sequential lung unit emptying on apparent carbon monoxide uptake can be corrected by expressing carbon monoxide concentration with respect to the inert gas, helium. Because the change in DL\textsubscript{CO} per alveolar volume that occurs over this small change in lung volume in normal human subjects is so small (28) and because the inert gas correction factor for sequential emptying has been shown to be theoretically accurate in normal subjects (2), we believe these assumptions are valid for our current analyses.

Second, we chose to measure carbon monoxide uptake only during the exhalation of 15% of the vital capacity (from 30 to 45% of exhaled vital capacity). In normal subjects, the relative contribution of various lung regions to the exhaled gas over this part of exhalation is not uniform at rest (33) and probably changes with position (19) and ventilation pattern (27, 30). Whether further changes may result from exercise, unrelated to ventilation changes, is unknown. Any such changes, however, would affect not only our measurement of DL\textsubscript{CO} but would also affect those made by the single-breath or steady-state techniques, both of which also sample only a portion of the exhaled vital capacity.

To eliminate the effects of ventilation pattern on our measurements, we held inspiratory and expiratory flows constant during all test maneuvers. We also measured exhaled inert gas concentrations during all test maneuvers to determine whether other factors were affecting gas distribution or emptying patterns. From these measurements, we found that gas distribution and emptying patterns were more uniform in the supine than in the sitting position, an observation consistent with others (19). We also found that the slope of the inert gas concentration during exhalation did not change significantly from rest to maximal exercise in either position, suggesting that exercise alone did not affect gas distribution or emptying patterns. Thus, although we may have sampled somewhat different lung regions in the sitting and supine positions (which would actually tend to decrease the difference between measurements in the sitting and supine positions because exhaled gas while the subject is supine would contain proportionally more gas from apical units), it appears that we sampled the same regions during exercise that we sampled at rest in each position.

Third, some errors common to other techniques of measuring DL\textsubscript{CO}, as noted previously, could also affect this technique. Excessive positive or negative intrathoracic pressure is known to affect DL\textsubscript{CO}, and during exhalation a constant airway pressure of 5 cmH\textsubscript{2}O was maintained by the subject. This amount of positive pressure, however, has been shown to have little effect on the measurement of DL\textsubscript{CO} (28). Hypoxemia at high exercise levels induced by the procedure may also influence carbon monoxide uptake. However, the respiratory maneuver in this technique lasts less than 5 s, and simultaneous exhaled oxygen tension measured during the test was never less than 91 Torr. The potential effect of carbon monoxide backpressure on measured DL\textsubscript{CO} was also negligible, as subjects never inhaled more than eight breaths of 0.3% carbon monoxide during any given testing period.

From the above, we believe that our results are an accurate reflection of carbon monoxide diffusing capacity at large lung volumes (but below total lung capacity) during rest and exercise. Because of the different lung volumes used and because our measuring technique is unique, our results are difficult to compare with those of others. Nevertheless, most workers agree that DL\textsubscript{CO} at rest in the supine position is greater than DL\textsubscript{CO} at rest in the sitting position (3, 4, 28) and that, in both positions, DL\textsubscript{CO} during exercise is greater than DL\textsubscript{CO} at rest (1, 4, 6, 8, 9, 12, 14–16, 29, 34). However, in the studies on normal subjects in whom multiple measurements of DL\textsubscript{CO} by either single-breath or steady-state techniques were made up to maximum work rates, there is disagreement on the pattern of this increase (i.e., linear vs. curvilinear) and whether or not a maximum DL\textsubscript{CO} is ever attained.

Considerations of the pressure-volume relationships of the pulmonary capillary bed are compatible with our observed curvilinear increase in DL\textsubscript{CO} during incremental exercise. As has been shown in rapidly fixed dog lungs (11), pulmonary capillaries are collapsed when perfusion pressure is zero, but their dimensions increase rapidly to 50-60% of maximum cross-sectional area when a critical opening pressure is exceeded (recruitment). Capillary cross-sectional area then increases more slowly to maximum as perfusion pressure is increased to 30-50 cmH\textsubscript{2}O (dilatation). If we use the known changes in pulmonary arterial and pulmonary venous pressures that occur with exercise (7), assume that human capillaries in a normal sized lung have pressure-volume relationships similar to those in dogs described above, and assume that changes in capillary volume and the alveolar-capillary membrane surface area are reflected by changes in DL\textsubscript{CO}, then the observed curvilinear increase in DL\textsubscript{CO} with exercise can be explained in the following way.

First, during mild exercise in seated subjects, increased pulmonary arterial pressure increases capillary inflow pressure. This increased pressure recruits capillaries in the upper parts of the lung that may be closed at rest. This results in a large increase in capillary volume and alveolar-capillary membrane surface area and, in turn, in DL\textsubscript{CO}. At higher work rates, with greater capillary perfusion pressures, capillary recruitment may approach a maximum, and further increase in DL\textsubscript{CO} can come only from capillary dilatation. Thus the rate of increase in DL\textsubscript{CO} would be slower.

The second mechanism for the greater increase in DL\textsubscript{CO} during mild exercise results from the pulsatility in
pulmonary arterial pressure. Since the pulmonary capillaries are very compliant, pulsatile inflow pressure will cause the capillaries to expand and contract as the heart beats. Thus, as inflow pressure increases during systole, capillary volume increases; as inflow pressure decreases during diastole, capillary volume decreases. This phenomenon has been indirectly documented by measurement of carbon monoxide uptake in a water-filled plethysmograph (25). Since our measurements of diffusing capacity represent carbon monoxide uptake from the capillary bed over several heartbeats, DLCO will reflect a time-weighted average of this pulsatile capillary volume

\[ V_c \cdot \text{dt}/\text{dt} \]

where \( V_c \) is capillary volume and \( t \) is time.

Theoretical consideration of the pulmonary vasculature suggests that heart rates between 60 and 120 beats/min will increase this time-weighted average of pulsatile capillary volume, regardless of increases in inflow pressure. This explanation depends on the assumption that the capillaries drain passively during diastole; i.e., the rate of draining is independent of heart rate. A study of pulsatile carbon monoxide uptake suggests that the capillaries take about 300 ms to drain at rest (25). The durations of systole and diastole (Table 2) indicate that there is ample time for the capillaries to drain during diastole at heart rates between 60 and 80 beats/min. However, at a heart rate of 100 beats/min, there is no longer enough time for the capillaries to drain before the onset of the next systolic pulse. This will result in an increased time-weighted average of pulsatile capillary volume. As heart rates rise above 120 beats/min, the arterial system severely dampens the pulsatility of the pulmonary arterial pressure (23). Consequently, the effects of pulsatility will contribute only to the increase in DLCO during mild exercise.

With the subject in the supine position, the relationship of inflow and outflow pressures to the top of the lungs changes profoundly. Capillary inflow and outflow pressures may now be adequate to recruit most of the capillaries with a resulting large increase in pulmonary capillary volume and alveolar-capillary membrane surface area and thus DLCO, even at rest. Exercise-induced increases in pulmonary vascular pressures, and heart rate in the supine position will affect the pulmonary capillary bed as described above. If the capillaries are already nearly maximally recruited at rest in the supine position, increases in DLCO can come only from capillary dilatation. Thus the increase in DLCO during mild exercise would not be as striking in supine subjects as in seated subjects. Furthermore, it is possible that a physiological maximum may be attained at work rates less than maximal under these conditions. That DLCO approaches a similar maximum in both the sitting and supine positions is not surprising, as the capillary bed may be maximally recruited and nearly maximally dilated in both positions at maximum work rates.

This model of the capillary bed during rest and exercise in sitting and supine positions is similar to that described by Danzert et al. (4) and is supported by experiments of Karp et al. (20) on perfused dog lungs exposed to varying inflow and outflow pressures. However, the simple concept that pulmonary capillary recruitment and dilatation alone explain the curvilinear increase in DLCO with exercise may not be complete. Increases in the membrane component of DLCO with increasing exercise may be produced by mechanisms other than capillary recruitment (16, 22). These increases may result from possible biochemical changes in the membranes or from changes in the plasma distance between the red blood cell and the membrane during exercise. Other factors that may affect DLCO during exercise include changes in the pulmonary capillary blood hematocrit and local reflexes or circulating substances associated with exercise that expose more of the capillary bed to pulmonary arterial pressure (3, 16).

The clinical implications of DLCO as measured during sitting and supine exercise are speculative. However, knowing the magnitude and pattern of increase in DLCO during exercise in seated and supine subjects might improve our ability to diagnose diseases of the pulmonary capillary bed. In particular, the increase in DLCO during mild exercise seems to depend on the character of the pulmonary arterial system, and the value for DLCO during supine exercise seems to depend on the total number of capillaries in the lungs. Therefore, measurement of DLCO during exercise might assist in the differentiation of arterial vascular disease (e.g., pulmonary emboli) from disease characterized by destruction of pulmonary capillaries (e.g., emphysema).

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TABLE 2. Cardiac timing during atrial pacing in humans

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<th>Duration of Systole, ms</th>
<th>Duration of Diastole, ms</th>
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<td>80</td>
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<td>120</td>
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</table>

HR, heart rate. *Calculated from the regression equation: systolic time = –1.2HR + 511 (21).
DIFFUSING CAPACITY DURING EXERCISE


