Restricted postexercise pulmonary diffusion capacity and central blood volume depletion

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Hanel, Birgitte, Inge Teunissen, Alan Rabøl, Jørgen Warberg, and Niels H. Secher. Restricted postexercise pulmonary diffusion capacity and central blood volume depletion. J. Appl. Physiol. 83(1): 11–17, 1997.—Pulmonary diffusion capacity for carbon monoxide (DLCO), regional electrical impedance (Z₀), and the distribution of technetium-99m-labeled erythrocytes together with concentration of plasma atrial natriuretic peptide (ANP) were determined before and after a 6-min “all-out” row in nine oarsmen and in six control subjects. Two and one-half hours after exercise in the upright seated position, DLCO was reduced by 6 (−2 to 21; median and range) %, the thoracic-to-thigh electrical impedance ratio (Z₀thorax/Z₀thigh) rose by 14 (−1 to 29) %, paralleled by a 7 (−3 to 11) % decrease and a 3 (−5 to 12) % increase in the thoracic and thigh blood volume, respectively. These responses were associated with a decrease in the plasma ANP concentration from 15 (13–31) to 12 (9–27) pmol/l (P < 0.05). Similarly, in the supine position, Z₀thorax/Z₀thigh increased by 10 (−5 to 28) % when DLCO was reduced 12 (6–26) % (P < 0.05), whereas DLCO remained stable in the control group. The increase in Z₀thorax/Z₀thigh and the corresponding redistribution of the blood volume in both body positions show that approximately one-half of the postexercise reduction of DLCO is explained by a decrease in the pulmonary blood volume. The role of a reduced postexercise central blood volume is underscored by the lower plasma ANP, which aids in upregulating the blood volume after exercise in athletes.

atrial natriuretic peptide; pulmonary blood volume; technetium-99m-labeled erythrocytes; regional electrical impedance

PULMONARY DIFFUSION CAPACITY for carbon monoxide (DLCO) is impaired after exercise of various durations and intensities (3, 8–10, 16, 20, 26–29). The postexercise reduction in DLCO reflects a decrease in both the membrane diffusion capacity and the pulmonary capillary blood volume (8). The maintained exercise arterial PO₂ and maximal O₂ uptake during repeated bouts of exercise together with the lack of an effect of furosemide argue for a causal role of a reduction in the central blood volume (8). In support of this, thoracic electrical impedance (Z₀), which is an index of fluid volume, is elevated after exercise (8, 29).

Marked changes in the central blood volume are reflected in plasma concentration of atrial natriuretic peptide (ANP). This is illustrated during head-up tilt, where the ANP plasma concentration decreases (18, 23), whereas it increases during exercise (5–7, 17, 22) and returns to the resting level within 1 h after exercise (7). At the onset of exercise, ANP release is controlled by atrial distension and by other stimulators thereafter (22). The magnitude of response is related to the intensity of exercise and is reduced in subjects with a higher blood volume and stroke volume and thereby is due to a smaller increase in atrial distension (6, 17, 22).

We hypothesized that the decrease in DLCO during recovery from exercise is due, in part, to a redistribution of the blood volume from the central vascular bed to more distal regions.

To test this hypothesis, we measured DLCO and regional Z₀ during exercise and during postexercise recovery. To estimate changes in central blood volume, we measured ANP by using the same protocol with different subjects. Other hormones, including arginine vasopressin (AVP), renin activity, aldosterone, and adrenocorticotropic hormone (ACTH), were also determined.

METHODS

Nine healthy male oarsmen and six other control subjects with no history of cardiovascular or pulmonary diseases participated in the study on blood volume distribution after exercise and another eight rowers in the study on hormone variables; six subjects of the latter study reappeared on a separate day for a control evaluation without rowing (Table 1). Each subject gave informed written consent, and the procedures were approved by the Ethics Committee of Copenhagen (KF 01–080/94).

Procedures

Study I. The subjects fasted for at least 3 h before entering the laboratory at 0800 and had refrained from vigorous exercise the day before the experimental day to normalize single-breath DLCO (29). All subjects rested supine for 30 min. Determinations of DLCO in the supine and upright seated positions were interspersed by a recovery period of 15 min to stabilize DLCO (2). A blood sample was drawn, and the erythrocytes were labeled with 99mTc. The labeled erythrocytes were separated in thoracic and thigh blood volumes by posterior recording of the activity from the thorax with a gamma camera. Similarly, thigh Z₀ was determined while the activity over the right thigh was recorded. After the subjects were stabilized for 15 min in the alternative position (supine or upright seated), the same measurements were repeated.

After a warm-up period at the subjects’ own pace, they performed a 6-min “all-out” row. Expired air was sampled for ventilation and O₂ uptake. The subjects then rested in the supine position for 2 h, after which the determinations of DLCO, Z₀, and the recordings by the gamma camera were repeated. Care was taken to ensure that the subjects remained in the same position before and after rowing, both
when seated and supine. The protocol was identical for the control subjects except for the rowing.

**Study II.** The sequence of rest, rowing, and recovery was the same for the study on hormone evaluation with eight additional rowers. Blood samples were obtained at the end of the respective periods from a catheter in the nondominant radial artery.

**Monitoring Equipment**

Single-breath DL_{CO} was assessed by using inspiration of a dilute mixture of CO, O_{2}, and He (13), and the rate of disappearance from the alveolar gas was calculated after a 10-s breath hold. The first 700 ml of the exhaled volume were discharged, and the following 600 ml were sampled. Inspiratory and expiratory concentrations of CO were measured with an infrared analyzer (MasterLab Jäger, Wurtzburg, Germany). The determination of He was based on the thermal conductivity principle (MasterLab) and was made in duplicate.

For regional Z_{0}, a body impedance monitor (BLM 2000, Aqua Medico) was used. Two electrodes (VL-00-S25, Medicotest) were placed on the right sternocleidomastoid muscle and two electrodes on the lower left ribs in the midclavicular line for thoracic Z_{0} (18). The outer two electrodes served for current and applied 10 mA at 2.5 and 100 kHz. They were spaced 5 cm from the inner voltage-sensing electrodes. Z_{0} was measured between the two inner electrodes. For thigh Z_{0}, one electrode was placed 5 cm superior to the patella and another 5 cm above the first. Two additional electrodes were placed 5 cm apart, 15 cm distal to the iliac crest.

A gamma camera with a rectangular, low-energy, high-resolution, parallel-hole collimator (General Electric) was used to image activity from the thorax and thigh. The energy was set to 140 KeV with a 20% window setting. Data were acquired as 5-min static acquisitions.

Ten milliliters of blood were drawn in a syringe containing heparin (20 IU/ml blood) and labeled with Sn^{99m}Tc pertechnetate. One milliliter of blood containing 406 (227–544) MBq was reinjected intravenously. After another 10 min, 10 ml of blood were drawn for the determination of the erythrocyte count rate and venous hematocrit. Total blood volume was determined by indicator dilution with the use of a TCK-11 kit for labeling of erythrocytes (Sn^{99m}Tc, CIS Bio International) and labeled with Sn^{99m}Tc pertechnetate (1). The count rate was measured on a gamma counter (Cobra 5010, Packard, CT), and hematocrit was determined in duplicate.

O_{2} uptake and ventilation were measured continuously with an Ergo-oxyscreen apparatus (Jäger). Heart rate was recorded from a Polar heart monitor (Vantage XL). Rowing was performed on a wind-braked ergometer (Concept 2, Morrisville, VT), and power was obtained from a computer (Concept 2).

Blood for hormone determination (20 ml) was taken in ice-cold polypropylene tubes containing heparin (20 IU/ml blood) and aprotinin (200 kIU/ml). Blood was kept in ice-cold water and centrifuged within 10 min at 4°C for 15 min at 3,000 revolutions/min. The plasma was stored at −20°C until the assays were performed. ANP and AVP were extracted from plasma by means of C_{18} cartridges (Sep-Pak, Waters) and determined by radioimmunoassay (RIA) (11, 31). Synthetic human hormones (Peninsula Laboratories, Belmont, CA) served as the reference preparation. Aldosterone was determined by solid-phase RIA in unextracted plasma (Coat-A-

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### Table 1. Values for age, weight, height, V̇O_{2max}, V̇E_{max}, HR_{max} and HR_{rest}, MAP_{rest}, and blood volume

<table>
<thead>
<tr>
<th>Study</th>
<th>Rowers (n = 9)</th>
<th>Controls (n = 6)</th>
<th>Study II (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25 (22–32)</td>
<td>22 (18–24)</td>
<td>26 (21–29)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87 (70–96)</td>
<td>78 (70–88)</td>
<td>79 (71–94)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>191 (184–197)</td>
<td>186 (179–198)</td>
<td>191 (179–197)</td>
</tr>
<tr>
<td>V̇O_{2max}, l/min</td>
<td>5.1 (5.0–6.1)</td>
<td>5.4 (4.6–6.2)</td>
<td>5.5 (4.9–6.2)</td>
</tr>
<tr>
<td>V̇E_{max}, l/min</td>
<td>188 (177–210)</td>
<td>190 (157–210)</td>
<td>181 (174–195)</td>
</tr>
<tr>
<td>HR_{max}, beats/min</td>
<td>193 (173–204)</td>
<td>193 (180–202)</td>
<td>181 (174–195)</td>
</tr>
<tr>
<td>HR_{rest}, beats/min</td>
<td>193 (173–204)</td>
<td>193 (180–202)</td>
<td>181 (174–195)</td>
</tr>
<tr>
<td>MAP_{rest}, mmHg</td>
<td>95 (78–106)</td>
<td>95 (78–106)</td>
<td>95 (78–106)</td>
</tr>
<tr>
<td>Blood volume, liters</td>
<td>6.86 (5.92–8.68)</td>
<td>6.05 (5.56–6.93)</td>
<td>6.05 (5.56–6.93)</td>
</tr>
</tbody>
</table>

Values are medians with range in parentheses; n, no. of subjects. V̇O_{2max}, maximal O_{2} uptake; V̇E_{max}, maximal ventilation; HR_{max} and HR_{rest}, maximal and at rest heart rate, respectively; MAP_{rest}, mean arterial pressure at rest.
Count, Diagnostic Products, Los Angeles, CA). ACTH was determined in unextracted plasma by RIA as previously described (12). Plasma renin activity was determined by use of the antibody-trapping method described by Poulsen and Jørgensen (25). Synthetic angiotensin I (Bio-Schwartz), which was tested against Research Standard A (Institute for Medical Research, Holy Hill, London, UK), served as a standard. The within-assay and between-assay coefficients of variation were 3.2 and 8.5%, respectively.

Data Analysis

The erythrocyte content in the regions of interest was calculated over an apical peripheral area of the lungs while activity from the heart, spleen, and kidney was avoided (Fig. 1). Similarly, a region over the thigh was sampled. The decay-corrected counts were calculated from the mean count (total counts divided by the area) and corrected with a calculation from the half-life of Tc (\(T_{\frac{1}{2}}\)), i.e., \(A_t = A_0 e^{-\frac{t}{T_{\frac{1}{2}}}}\), where \(\lambda = \ln(2)/T_{\frac{1}{2}}\), \(A_t\) is activity at time \(t\), and \(A_0\) is activity at time 0, and the ratio between the thorax and thigh mean counts was used as a measure for erythrocyte distribution before and after rowing.

Despite the physical decay-corrected mean counts, we saw a reduced mean count in the control subjects compared with that in the rowers. This decrease was of the same magnitude in the thorax and thigh (11 and 13%, respectively) when subjects were seated in contrast to being in the supine position, where a larger reduction in the thoracic mean count (17%) took place compared with the thigh (7%). Besides the physical decay, we cannot exclude the biological decay.

![Fig. 2. Pulmonary diffusion capacity of carbon dioxide (DLCO) Pre and Post ~2 h of rowing (Rowers; \(n = 9\)) and maintained rest (Controls; \(n = 6\)) in supine and upright seated positions. ■ and horizontal lines, Mean and median, respectively; ●, minimum and maximum. *P < 0.05 compared with Pre.]
decrease of ~10% in physical decay-corrected activity was observed in the first 3 h by using the TCK-11 kit (T. B. Lindhardt, personal communication; Ref. 15). This is in agreement with our findings in the control subjects. Thus the decrease due to labeling instability accounts for the computed biological decay.

Similarly, a ratio between thoracic and thigh Z₀ was calculated to compare changes in the distribution of fluid. Z₀ was determined for both a high (100-kHz) and low (2.5-kHz) frequency (19). Two frequencies of current were used to detect changes occurring in separate fluid compartments. The cells are conductive only with a high-frequency current, whereas the extracellular compartment selectively is conductive when a low-frequency current is applied (10, 33). Regional Z₀ was recorded every minute and expressed as the average for 5–7 min.

Values are expressed as median with range. Changes with time in rowers and control subjects were located by Pratt's modification of the one-sample Wilcoxon test, whereas the Mann-Whitney test was applied for unpaired data (32). P < 0.05 was considered significant. Because measured responses failed the standard normality test, we analyzed our data by using a nonparametric statistic. Sample size was sufficient on the basis of power analyses for expected differences in DLCO, mean counts, Z₀, and ANP.

RESULTS

In the supine position, DLCO decreased by 12 (6 to 26) % after exercise (P < 0.01) (Table 2, Fig. 2). At 2.5 kHz, Z₀ increased 6 (~4 to 16) % over the thorax, but it
was unchanged over the thigh. Conversely, at 100 kHz, $Z_0$ was unchanged over the thorax but decreased by 7 (−4 to 20) % over the thigh. Thus the individual value for the ratio between thoracic and thigh $Z_0$ increased for both 2.5 and 100 kHz [11 (−5 to 28) and 9 (−2 to 27) %, respectively] (Fig. 3). Thoracic and thigh mean counts decreased 14 (0–24) and 7 (−24 to 20) %, respectively ($P$, 0.01), and their ratio was reduced by 8 (−21 to 19) %.

In the upright seated position, $DL_{CO}$ decreased 6 (−2 to 21) % after exercise ($P < 0.01$) (Table 2, Fig. 2). At 2.5 kHz, $Z_0$ increased by 7 (1–16) % over the thorax and decreased by 9 (1–40) % over the thigh. At 100 kHz, $Z_0$ increased by 6 (−1 to 30) % over the thorax and decreased by 10 (0–18) % over the thigh ($P < 0.01$). Thus the ratio between thoracic and thigh $Z_0$ increased both at 2.5 and 100 kHz [by 14 (8–22) and 14 (1–29) %, respectively ($P < 0.01$)] (Fig. 3). Thoracic and thigh mean counts decreased by 18 (8–22) and 10 (2–18) %, respectively, and their ratio by 9 (−5 to 13) %.

Control Subjects

In the supine position, $DL_{CO}$ was unchanged in the same time periods as reported for the rowers (Table 2). Both at 2.5 and 100 kHz, thoracic and thigh $Z_0$ were unchanged and thereby also their ratio (Fig. 3). Thoracic and thigh mean counts decreased 17 (7–33) and 7 (1–21) %, respectively ($P < 0.01$), and resulted in a 9 (−3 to 15) % decrease in their ratio.

Also, in the seated position, $DL_{CO}$ remained unchanged (Table 2), as did thoracic and thigh $Z_0$ both at 2.5 and 100 kHz and thereby their ratio (Fig. 3). Thoracic and thigh mean counts decreased by 11 (−3 to 25) and 13 (12–22) %, respectively, resulting in a statistically unchanged ratio.

The hormonal response to exercise was distinct, with three- to eightfold increases in plasma ANP, AVP, aldosterone, ACTH, and renin activity (Table 3, Fig. 4). During the recovery, AVP and aldosterone returned to the resting level, whereas plasma renin activity remained elevated and ANP and ACTH were reduced to a level lower than at rest. In the control study, no statistically significant changes were noted.

DISCUSSION

This study confirmed that pulmonary diffusion capacity decreases during recovery from a short exercise bout and demonstrated that this is the case when determined in both a supine and an upright seated position (8, 9, 16, 26, 27, 29). Our data suggest that at the same time as the decrease in diffusion capacity, a significant shift of fluids occurred from the thorax to the peripheral vascular space. Moreover, the reduction in central blood volume after exercise was associated with a reduction in the plasma concentration of ANP.

In the control subjects, $DL_{CO}$ and the ratio between thoracic and thigh $Z_0$ in both body positions were unchanged. When the control subjects were seated, the ratio between thoracic and thigh mean counts and the thoracic and thigh $Z_0$ values were unchanged, whereas with subjects in the supine position the mean counts and thoracic and thigh $Z_0$ values were reduced 9% with no changes in $Z_0$, indicating that a mean counts ratio is a less reliable indicator of blood volume shifts in the supine than in the sitting position.

We hypothesized that the decrease in $DL_{CO}$ 2 h after exercise is associated with a redistribution of the blood volume. Although the $DL_{CO}$ in the control subjects was unaffected, the mean counts over the thorax decreased in the supine position, suggesting that other mecha-
nisms play a role in regulating the lung capillary volume in the hours after rowing. In the supine position, $D_{LCO}$ was 20% larger than in the sitting position, both for the rowers and the control subjects, reflecting a larger central blood volume, as supported by a larger thoracic $Z_0$ (Table 2). A possible explanation for the unaffected $D_{LCO}$ in control subjects in the supine position could be a $D_{LCO}$ reserve that is large enough to maintain $D_{LCO}$ in the face of small changes in lung capillary volume.

The rise in thoracic $Z_0$ (2.5 kHz) in the supine position implies that extracellular thoracic fluid volume had diminished, and the corresponding drop in similar magnitude in thigh $Z_0$ (100 kHz) means that the amount of extra- and intracellular fluid in the leg was enlarged. This could be interpreted as a shift of plasma volume from the chest to the legs, with a proportional increase of leg blood volume. We see similar results in the sitting position. The magnitude of the rise in thoracic $Z_0$ (2.5 kHz) and the corresponding drop in thigh $Z_0$ (2.5 kHz) when seated was comparable to changes seen in the supine position and underscores the distal fluid shift. The increase in thoracic $Z_0$ and drop in thigh $Z_0$ (100 kHz) point to the portion of the distal fluid shift located within the cells (19). The increase in thoracic-to-thigh ratios for both frequencies in both body positions indicates that fluid, either intra- or extracellular, had moved from the thorax to the leg, thus indicating a volume shift in the vascular space and thereby a distribution of blood from thorax to thigh after rowing (19).

One methodological concern when $99m$Tc tracer is used is to correct for physical decay. An additional concern is the apparent biological decay (see Table 2) in the control subjects. When the biological decay is taken into account, the reduction in mean counts in the rowers when seated results in a 7% decrease and a 3% increase in thoracic and thigh blood volume, respectively. In the supine position, the biological decay makes it difficult to see any changes in mean counts caused by rowing. The reduction of thoracic mean counts in control subjects, but with no change in the legs, is puzzling. Of note is that thoracic $Z_0$ was unchanged, which suggests only very small shifts in blood volume.

We speculated on the extent to which the reduction in $D_{LCO}$ was caused by increased resistance to diffusion from the alveolar membrane (Dm). On the basis of our recent data, where $D_{LCO}$ was measured in the seated position at two inspired O$_2$ concentrations to calculate Dm and the capillary blood volume 2 h after exercise (8), we estimate that a 6% decrease in $D_{LCO}$ is associated with a 7% reduction in the central blood volume, which corresponds to a 4% reduction in Dm. Because thoracic $Z_0$ at both frequencies increased after rowing, we can exclude interstitial edema formation but not a capillary failure (34) induced from exercise as an explanation for the postexercise reduction in $D_{LCO}$ (4, 8, 16, 20, 21, 27, 29). We therefore conclude that the major part of the reduced $D_{LCO}$ after rowing can be explained by a blood volume shift from the chest to the legs.

The small but significant postexercise decrease in ANP suggests that even minor decreases in venous return are detected by the stretch receptors of the right atrium (24). Taken together with an increased thoracic-to-thigh $Z_0$ ratio at both 2.5 and 100 kHz and a decreased mean counts ratio, the reduction in $D_{LCO}$ postexercise is similar to that seen in head-up tilt studies when blood pressure is maintained (30). In our study, heart rate and mean arterial pressure were at resting values postexercise (Table 1), whereas both heart rate and mean arterial pressure increased in the condition of 30° head-up tilt (30). This mechanism of a slight reduction in ANP is a useful upregulation of the extracellular volume and blood volume in the hours after exercise.

Endurance athletes have a larger total blood volume (14). At the same time, this study indicates that they have a reduced central blood volume in the recovery period. If the reduction in $D_{LCO}$, which lasts up to 24 h (29), reflects a decrease in lung capillary blood volume, one could speculate that reduction in central blood volume is associated with a decrease in ANP, not only 2 h after exercise but also in parallel with the reduced $D_{LCO}$.

This recovery response could explain the persistent reduction in $D_{LCO}$ that apparently has little effect on exercise responses during a repeated row (8). This indicates that $D_{LCO}$ is very sensitive to changes in the lung capillary volume. Moreover, it appears that the smaller central blood volume is sensed, causing a decrease in ANP to upregulate the central blood volume and thereby the total blood volume.

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