Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure

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In CHRONIC HEART FAILURE (CHF), ventilation inefficiency, as indicated by the increased slope of the ratio of ventilation (Ve) to CO2 output (VCO2) (3), correlates with dyspnea and reduced aerobic performance (4, 5), two hallmarks of the syndrome. This is not sufficiently explained by abnormalities in central hemodynamics, and a role of additional factors in causing exercise hyperventilation has emerged (7, 27). Suggested mechanisms are as follows: ventilation-perfusion (V/Q) mismatch (28, 31), changes in respiratory musculature (25) that produce a need for excessive ventilatory effort, abnormalities in endothelial and working muscle function leading to early acidosis and increased muscle CO2 release (26), and stimulation of arterial chemoreceptors and afferent fibers originating from muscular receptors sensitive to local metabolic products (i.e., ergoreceptors) (7, 26).

More recently, in CHF, a relation has been established between exercise hyperpnea, reduced aerobic capacity, poor prognosis, and impaired gas diffusion across the alveolar-capillary membrane (15, 17, 19, 27, 30). Nevertheless, in the interpretation of normalization of the slope relating Ve to VCO2 and of decrease in the perceived sense of dyspnea that occurs with physical training, an improvement in lung diffusing capacity has been neglected. This, however, does not seem to be an unrealistic possibility, because, in CHF, training produces a systemic amelioration in endothelial function (23, 24) that involves the pulmonary vessels (20). Paracrine agents released by the endothelium participate in the control of pulmonary vessel tone and permeability and of the resistance to O2 transfer from the alveolus to its uptake by hemoglobin (14).

We aimed at probing whether, in CHF, exercise training therapy increases the alveolar-capillary membrane diffusing capacity; this effect correlates with an improvement in systemic endothelial function, and it may contribute to increased exercise performance.

METHODS

Study population. Thirty-eight men, ≤65 yr old, with compensated CHF due to left ventricular dysfunction (average left ventricular ejection fraction = 35 ± 4%), were randomized to the exercise-training (n = 20) or control (n = 18) group. Two patients in the trained group and two in the control group were excluded because of instability in exercise tolerance in the pre-study interval; two patients in the trained group and one in the control group were excluded because of poor compliance. Therefore, 16 trained and 15 untrained patients who completed the trial were considered in the data analysis. Randomization was performed according to a randomization list generated by computer. Patients were recruited from the Heart Failure Clinic at San Paolo Hospital. The hospital’s ethics committee approved the study. All patients were willing to participate in the trial, and written, informed consent was obtained from each of them after explanation of the nature of the study and of the possible clinical benefits and risks.

Inclusion criteria were New York Heart Association class II or III, a left ventricular ejection fraction at rest of ≤40%, as assessed by echocardiography, no change in drug treatment in the 4 wk preceding randomization, and abstinence from tobacco products for ≥9 mo before enrollment. Twelve participants had never smoked. Patients were not recruited if they had had myocardial infarction in the previous 6 mo; if they had significant valvular heart disease, hypertension, diabetes mellitus, hypercholesterolemia, pulmonary disease, atrial fibrillation, angina pectoris at rest or on exercise, peripheral
vascular disease, or musculoskeletal abnormalities precluding exercise training; if they were taking lipid-lowering agents or antioxidant vitamins; or if they were participating in a regular exercise program.

Patients were classified as having ischemic cardiomyopathy (previous myocardial infarction or angiographic evidence of coronary artery disease that could explain the extent of cardiac impairment) or dilated cardiomyopathy (left ventricular enlargement and dysfunction of unknown origin).

**Study design.** The study design is depicted in Fig. 1. The study comprised a 4-wk prestudy interval and a 16-wk study period. The prestudy interval was aimed at documenting stability of clinical condition, drug treatment, and exercise tolerance. A cardiopulmonary exercise test (CPET) (1) was performed at the beginning (test 1) and end (test 2) of the prestudy interval. Soon after completion of test 1, patients were randomized to the training or the control group, and the assignment was sealed in an envelope until test 2 was completed. Those performing the tests were blinded to the patient’s assignment. The second exercise test was preceded by an evaluation of brachial artery endothelial function and pulmonary function, in that order, with ≥60 min between the tests. The same procedures were repeated at 8 wk (test 3) and 16 wk (test 4) in the trained and untrained groups. The last 10 patients in both groups underwent hemodynamic monitoring during exercise tests 2, 3, and 4. All tests were carried out in the morning after an overnight fast. Patients’ physicians were requested to inform the investigators in case of necessity of changes in the therapeutic regimen. Control patients were encouraged to maintain their normal daily activity, not to follow any exercise regimen, and to attend the outpatient clinic every 2 wk for assessment of compliance (records were taken by the supervisor cardiologist of the patients’ attendance, duration of the warm-up, aerobic, and cool-down phases, and exercise intensity), cardiac-related symptoms and signs, and avoidance of regular exercise activity. All subjects were encouraged not to change their smoking habit during the course of the study.

**Exercise training.** Electromagnetically braked stationary cycles were used as exercise equipment; the duration of each exercise-training session was 40 min; during each session, patients completed a 5-min warm-up phase, a 30-min aerobic phase, and a 5-min cool-down phase; patients attended the exercise-training program four times per week. According to the heart rate reserve method (1), exercise intensity was set at 60% for the first 2 wk and then increased, as tolerated, to as high as 80%. All sessions were held at the hospital gymnasium under medical supervision. After the 8-wk training period, the patients were asked to avoid exercise (detraining) for another 8 wk, during which they attended the outpatient clinic every 2 wk for assessment of cardiac symptoms and questioning about abstinence from physical activity.

**CPET analysis.** Each patient performed a supervised, standard, progressively increasing (personalized ramp protocol) work rate (WR) CPET to maximum tolerance on a cycle ergometer. Gas exchange measurements (cardiopulmonary metabolic cart, Sensormedics Vmax Spectra) were obtained at rest (3 min), during 2 min of unloaded cycling at 60 rpm followed by a progressively increasing WR exercise, and at 3 min of recovery. Heart rate (HR), 12-lead electrocardiogram, and cuff blood pressure were monitored and recorded. Venous (V̇E, BTPS), O2 uptake (V̇O2, STPD), CO2 uptake (V̇CO2, STPD), and other exercise variables were computer calculated breath-by-breath, interpolated second-by-second, and averaged in 10-s intervals (35).

Ventilatory efficiency was assessed by calculating the slope of increase in V̇E with respect to V̇CO2. The V̇E/V̇CO2 slope was measured by linear regression, with the nonlinear part of the data after the onset of ventilatory compensation for metabolic acidosis excluded (32). The slope of V̇CO2 at the anaerobic threshold (AT) and the rate at which V̇O2 increased per work rate (ΔV̇O2/ΔWR), as an indicator of aerobic efficiency (34), were also measured. ΔV̇O2/ΔWR was calculated for the progressively increasing exercise period, beginning 1 min after WR started to increase. The 1-min delay after the start of increase in WR was used to take into account the time constant for V̇O2 to respond to the increasing WR (−35 s for normal subjects) (35). Peak V̇O2 was determined by the highest V̇O2 achieved during exercise. Age- and weight-adjusted V̇O2 values were also determined (35). The maximal O2 pulse was measured by dividing the highest V̇O2 by the simultaneous HR. The dead space-to-tidal volume ratio was derived by using arterial PcO2 according to the standard formula (18). The alveolararterial P02 difference (A-aO2) was measured from the alveolar gas equation (1).

**Hemodynamic measurements.** After sterile preparation procedure, a 5-F thermodilution double-lumen balloon-tipped catheter was inserted into an antecubital vein and positioned into the pulmonary artery under fluoroscopic guidance. After the sheath was secured, the patient was helped off the catheterization table and onto an upright cycle ergometer. After a 15-min rest period, baseline upright values, including right atrial, pulmonary arterial, and pulmonary wedge pressures, cardiac output (thermodilution, in triplicate, with the 3 measurements averaged), hemoglobin, and plasma protein concentrations, were obtained. Systemic vascular resistance (dyn·s·cm⁻⁵) and pulmonary arteriolar resistance were calculated as the ratio of mean systemic arterial pressure minus mean right atrial pressure and mean pulmonary arterial pressure minus mean wedge pulmonary pressure, respectively, to cardiac output.

At peak exercise, hemodynamic measurements were repeated in an orderly fashion. Blood gases (arterial P02 and Pco2) and pH were determined at rest and immediately before the end of exercise on arterialized capillary blood samples from the hyperemic earlobe. We did not correct arterial blood gases for actual body temperature but, rather, assumed a body temperature of 37°C.

**Pulmonary function.** Spirometry was performed with equipment that met the American Thoracic Society performance criteria (2). To adjust for height, age, and gender, we used published prediction equations for forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) (21). Diffusing lung capacity for CO (DlCO) was determined twice with washout intervals of ≥4 min (the average was taken as the final result) with a standard single-breath technique. The

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**Fig. 1.** Study design.
maneuver was performed using a test gas with 0.28% CO-0.30% methane-21% O2-balance N2. DLCO subdivisions, i.e., the alveolar-capillary membrane diffusion capacity (Dm) and the capillary pulmonary blood volume available for gas exchange (Vc), were determined according to the classic Roughton and Forster method (29).

This method partitions pulmonary diffusing capacity into its component resistances, the diffusive resistance of the alveolar-capillary membrane (1/Dm) and the reactive resistance due to pulmonary capillary blood (1/θ Vc, where θ is the rate of reaction of CO with hemoglobin), according to the following equation

\[ \frac{1}{D_{LCO}} = \frac{1}{D_m} + \frac{1}{1/\theta V_c} \]

The 1/θ value was determined using the following equation, which assumes that the red cell membrane has a negligible resistance to gas exchange: 

\[ \frac{1}{\theta} = \frac{14.6}{Hb} \times \left(0.001 \times P_{A CO_2} + 0.0134\right) \]

where Hb is the subject’s hemoglobin concentration (g/dl) and P A CO 2 is alveolar P O 2 . When DLCO is measured at different inspiratory O2 fractions (20, 40, and 60%), a plot of 1/DLCO vs. 1/θ will yield a straight line with a y-intercept of 1/Dm and a gradient of 1/θVc. The single-breath alveolar volume (V A ) was derived by methylene dilution. DLCO, Dm, and Vc were expressed in absolute values, as well as per unit of V A (DLCO/V A , Dm/V A , and Vc/V A ).

Vascular studies. Vascular assessments were performed according to the guidelines of the International Brachial Artery Reactivity Task Force (8). Imaging studies of the brachial artery were performed with a high-resolution ultrasound Hewlett-Packard 11-MHz linear-array transducer. The monitored, nondominant arm was positioned at heart level, with the distal forearm supinated and immobilized by support encompassing the limb. After the clearest view of the brachial artery was found, anatomic landmarks were noted, the skin was marked, and the arm was kept in the same position to maintain the same image of the artery. Ultrasound images were obtained by the same investigator throughout the study. Blood flow-mediated vasodilation was assessed by measurement of the maximal change in diameter of the brachial artery during reactive hyperemia created by an inflated cuff (50 mmHg above systolic pressure for 5 min) on the forearm. Arterial diameter was measured in millimeters from the artery-blood interface on the anterior and posterior wall, coincident with the R waves on the electrocardiogram, for five cardiac cycles, with these five measurements averaged. Patients were rested in a supine position for 15 min before the first baseline measurement. Then the cuff was inflated for 5 min and rapidly deflated. A second scan was taken for 90 s after deflation, with measurements taken 15, 30, 60, and 90 s after deflation. Maximal changes were recorded 30 s after cuff release. After a 10-min rest period, a further baseline measurement was recorded, and 300 µg of nitroglycerin (NTG) were administered sublingually. A final brachial artery recording was then made after 5 min. The image analysis and measurement of the vasodilator response from repeated studies were performed by an individual who was blinded to the sequence.

Statistical analysis. Patient characteristics at baseline were compared using an unpaired t-test or Fisher’s exact test. Repeated-measures analysis of variance was used to determine whether a significant (P < 0.05) difference in the change across time occurred between the two groups. For variables for which a significant time × group interaction was observed, analysis of variance was used to assess a within-group time effect, and Student’s two sample t-test was used to assess a group effect with Bonferroni’s adjustment. The relation between changes in DLCO and Dm and those in peak VO2 and that between changes in brachial artery diameter and changes in DLCO and Dm were assessed using Pearson’s coefficient of correlation. Values are means ± SE. Statistical analyses were performed by means of Stata 7.0 software package (Stata, College Station, TX).

RESULTS

Trained and untrained patients had similar baseline characteristics and drug regimen distribution (Table 1). In both groups, FEV1 and FVC were not consistent with airway obstruction (Table 2); ejection fraction was reduced (Table 3); peak VO2 was compromised; the VE/VCO2 slope was increased, exceeding the value of 30 (the upper normal limit), which is typical of CHF patients (3, 4, 32); and ∆VO2/ΔWR, which reflects the O2 utilized per unit increase in WR and is an index of aerobic efficiency, was around the lower normal limit of 8.6 (35) (Fig. 2). In the study group, DLCO and DLCO/V A were reduced to 79 ± 4 and 77 ± 6% of predicted normal values (21) compared with 81 ± 5 and 79 ± 4% in the control group (Fig. 3, Table 2). Brachial artery flow- and NTG-mediated vasodilation were comparable in the two groups (Fig. 4). As shown in Table 3, baseline hemodynamic variables, A-ADo2, plasma hemoglobin, and protein concentrations at rest and at peak exercise were similar between the groups.

Drug distribution included diuretics, digoxin, a β-adrenergic receptor blocker, and an angiotensin-converting enzyme inhibitor (Table 1). During the 16-wk study, there were minor changes in medications. In the exercise-training group, the dose of diuretic was increased in one patient, the dose of β-receptor blocker was reduced in two patients, and digoxin therapy was discontinued in one patient. Among untrained patients, the dose of angiotensin-converting enzyme inhibitors was reduced in two cases, the dose of diuretic was increased in three cases, and digoxin was withdrawn in two patients.

Compared with baseline, at 8 wk of follow-up, there were no significant changes in any of the examined variables in the untrained group at rest and during peak exercise (Tables 2 and 3, Figs. 2–4). On the contrary, in the trained patients, we detected an increase in DLCO (25%, in all but 2 patients), Dm (15%, in all but 1 patient), Vc (+10%; Fig. 3), DLCO/V A (+25%), Dm/V A (+14%), Vc/V A (+13%; Table 2), peak VO2 (+13%), VO2 at AT (+20%), peak O2 pulse (+13%), ∆VO2/∆WR (+15%; Fig. 2), and flow-mediated percent increase in brachial artery diameter (from 4.8 to 8.2%, P < 0.01; Fig. 4); a decrease of VE/VCO2 slope (−14%); and no change in the ratio of dead space to tidal volume (Fig. 2), FEV1, FVC (Table 2), and NTG-mediated brachial artery
vasodilation (Fig. 4). All the reported changes were significant compared with baseline values in these patients and the corresponding values in the untrained group. At rest, there was a trend toward an increase in cardiac output in stroke volume (P = 0.092) and toward a decrease in pulmonary arteriolar resistance (P = 0.083) compared with baseline. Stroke volume was significantly greater (P < 0.05) and pulmonary arteriolar resistance was significantly lower (P < 0.05) than in controls (Table 3). At peak exercise, cardiac output and stroke volume were greater and systemic vascular resistance and pulmonary arteriolar resistance were lower with training than before training and in the control group. Physical training was also associated with a significant reduction of A-aDO₂ at rest. At peak exercise, there was an increase in A-aDO₂ in both groups that was significantly smaller in the trained group (Table 3).

Variations from baseline with training in peak VO₂ correlated significantly with those in DLCO and DM (Fig. 5; r = 0.58, P = 0.019 and r = 0.51, P = 0.04, respectively), and changes in DLCO were related to those in variations from baseline with training in peak VO₂ and A-aDO₂ at rest. At peak exercise, there was an increase in A-aDO₂ in both groups that was significantly smaller in the trained group (Table 3).

At the end of an 8-wk detraining interval, values of DLCO, DM, Vc, peak VO₂, A-aDO₂, VO₂ at AT, V̇E/V̇CO₂ slope, ∆VO₂/∆WR, O₂ pulse, cardiac output, stroke volume, systemic and pulmonary capillary blood volume. *P < 0.01 vs. baseline. †P < 0.05 vs. untrained.

Table 3. Hemodynamics, ejection fraction, hemoglobin and plasma protein concentrations, A-aDO₂, and body weight

<table>
<thead>
<tr>
<th></th>
<th>Trained</th>
<th>Untrained</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8-wk follow-up</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>76.4 ± 2.5</td>
<td>75.3 ± 2.3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78 ± 12</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>99.6 ± 10</td>
<td>98.3 ± 11</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.14 ± 0.6</td>
<td>4.35 ± 0.9</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>52.1 ± 9.5</td>
<td>57.8 ± 7.8 †</td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td>27.2 ± 4.5</td>
<td>25.3 ± 4.9</td>
</tr>
<tr>
<td>Mean PWP, mmHg</td>
<td>20.4 ± 2.2</td>
<td>18.5 ± 2.3</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1.83 ± 137</td>
<td>1.73 ± 152</td>
</tr>
<tr>
<td>PAR, dyn·s·cm⁻⁵</td>
<td>151.2 ± 23</td>
<td>126.5 ± 13 †</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>35.3 ± 3.3</td>
<td>36.1 ± 3.1</td>
</tr>
<tr>
<td>Hb concn, g/dl</td>
<td>14.5 ± 0.6</td>
<td>14.4 ± 0.8</td>
</tr>
<tr>
<td>Plasma protein concn, g/dl</td>
<td>7.0 ± 0.7</td>
<td>6.9 ± 0.5</td>
</tr>
<tr>
<td>A-aDO₂, mmHg</td>
<td>9.3 ± 1.8</td>
<td>5.2 ± 1.3 †</td>
</tr>
</tbody>
</table>

Values are means ± SE. Hemodynamic measurements were performed in the last patients in both groups. MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PWP, pulmonary wedge pressure; SVR, systemic vascular resistance; PAR, pulmonary arteriolar resistance; LV, left ventricle; A-aDO₂, alveolar-arterial O₂ difference. *P < 0.05 vs. baseline. †P < 0.05 vs. untrained. ‡P < 0.05 vs. rest.
pulmonary arteriolar resistance, and brachial artery flow-mediated vasodilation were comparable to those at baseline and were not significantly different from those in the untrained group at the end of follow-up.

There were no changes in smoking habit, body weight, or hemoglobin and plasma protein concentrations in the course of the study.

No untoward events occurred during exercise testing or training procedures.

DISCUSSION

Ventilatory control can be considered to be normal in CHF patients, but ventilatory efficiency is impaired (31). Robin and collaborators (28) first suggested that this might be due to V/Q mismatch. In normal subjects, there is some V/Q mismatch due to the effects of gravity (36), which unavoidably results in an A-aDO₂. The difference is small at rest and increases during exercise (9) and may be related to V/Q mismatch, shunt, or diffusion limitation (6). Exercise V/Q mismatch does not sufficiently justify the observed increase in A-aDo₂. Shunting is also not an important component in normal humans (12). It appears that diffusion limitation, possibly due to reduced transit time of red blood cells through the lung capillaries, may cause the A-aDO₂ seen on exercise in healthy individuals (9, 33). Little work has been done on these mechanisms in heart failure.

The present study reports three major findings. 1) In CHF patients, exercise substantially increased A-aDO₂, which, as a function of peak VO₂, was greater than in normal individuals (22). 2) Physical training significantly improved lung diffusing capacity at rest, a determinant of aerobic efficiency (17, 27, 30), mainly through an increase in DM. A cause-effect relation linking training with DLCO improvement is supported by two observations: the control group did not show any changes in lung diffusing capacity during follow-up, and this effect was lost with detraining. 3) Changes in DLCO were associated with a significant reduction in A-aDO₂ at the same workload. It cannot be established whether this also reflects an improvement in exercise-induced hypoxemia because of lack of measurements of actual in vivo arterial blood temperature. Calculation of O₂ saturation is based on measured arterial PO₂ and changes in body temperature and pH.

What are the mechanisms underlying the improvement in alveolar-capillary membrane conductance? DLCO, DM, and Ve may have been increasing simply because of higher cardiac output and better diffusion-perfusion matching after training. Because DLCO, DM, and Ve vary directly with cardiac output, any intervention that increases cardiac output will also secondarily increase DLCO, DM, and Ve without implying any intrinsic change of the alveolar-capillary membrane. This would have been better proved if, in addition to measurements at rest, DLCO and cardiac output were measured at the same time at exercise. Lack of these measurements is a basic limitation, which was due to the difficulties of many of these CHF patients with breath holding during maximal exercise.

Fig. 2. O₂ uptake (peak VO₂), VO₂ at anaerobic threshold (VO₂AT), O₂ pulse, dead space-to-tidal volume ratio (Vd/VT), slope of the ratio of ventilation (VE) to CO₂ production (VE/VO₂ slope) and change in VO₂-to-change in work rate ratio (∆VO₂/∆WR), at baseline (week 0), at the end of training (8 wk), and after detraining (16 wk).
This interpretation, however, would not explain the $D_M$ improvement and A-aDo$_2$ reduction at rest after training, because cardiac output before and after training was unchanged. The gas conductance properties of the alveolar epithelium and capillary endothelium and the length of the diffusion path for gas exchange are two major $D_M$ determinants. The diffusion path generally varies in parallel with the amount of fluid in the alveolar-interstitial space as a result of a balance of osmotic and hydrostatic forces and transport of Na$^+$ from blood to interstitium. Exercise training was not associated with
significant variations in osmotic (plasma protein concentration) and hydrostatic forces (pulmonary arterial, pulmonary wedge, and right atrial pressures and ejection fraction). Thus alternative interpretations for the improved DL CO with training may be an increase in D M properties or a downregulation of Na\(^+/H^+\) and fluid transport from the capillaries to the alveolar interstitial space. The same mechanisms underlying these effects could increase V\(_c\) by producing greater pulmonary vasodilation or better capillary recruitment at any given cardiac output. In this respect, it is significant that a positive correlation was found between changes in DL CO and D M , which might suggest that the factors that increase the endothelium-mediated vasodilating properties at the periphery are the same as those that facilitate O\(_2\) diffusion. We can only speculate on the mechanisms linking regular aerobic exercise and pulmonary gas transfer in CHF patients. Repeated episodes of increased blood flow with exercise or metabolic effects of training may be the basis for a chronic stimulus to the release of endothelial paracrine agents that control vascular tone and permeability. These effects may not be confined to the exercising limbs (5, 23, 24) but would be imposed throughout the vasculature, including the lung, the only organ receiving the whole cardiac output.

Did facilitation of gas transfer across the alveolar-capillary interface affect ventilatory efficiency and exercise VO\(_2\)? An improvement of systemic endothelial function and perfusion to working muscles, as well as an increase in cardiac output and O\(_2\) pulse on exercise, can well explain the benefits of training on VO\(_2\) (7, 11, 24, 25). However, in this study, a positive correlation was found between changes in DL CO and changes in peak VO\(_2\). Although this might simply reflect association, a few compelling comments are in order. In CHF, exercise raises the capillary-pulmonary pressure and the fluid-flow transition (factors that underlie alveolar-capillary stress failure) (37), the physiological increase of lung diffusion during exercise is limited (impeded increase in conductance because of excessive fluid filtration to alveolar interstitium), and the capillary recruitment for gas exchange is inadequate (14). In this setting, hyperventilation might help keep alveolar Po\(_2\) within normal limits but could precipitate premature exhaustion of the ventilatory reserve (27) and early exercise termination. Consistent with these interpretations are the correlations observed in CHF patients between peak VO\(_2\) and lung diffusion (17, 27, 30), as well as the acute decrease of peak VO\(_2\) and ventilatory efficiency (steeper V\(_E\)/V\(_\text{CO}_2\) slope) after an acute D M reduction (15). These considerations support the hypothesis that in CHF an impairment in lung diffusion capacity is involved in peak VO\(_2\) limitation and ventilatory inefficiency and that there is a link between changes in lung function and improvement in exercise performance with physical training (6, 26, 38). On the other hand, the increase in VO\(_2\) at AT (delayed reliance on

Fig. 5. Changes in DL\(_{co}\) and D M vs. changes in peak VO\(_2\) and changes in flow-mediated increase in brachial artery diameter vs. changes in DL\(_{co}\) and D M with physical training.
an aerobic pathways for energy production) and in $\Delta VO_2/\Delta WR$ (potentiated aerobic efficiency) indicates a favorable interaction of regular exercise training with more than one mechanism sustaining the increased $V_e/VCO_2$ slope in these patients. A less distended interstitial space and a reduced activation of J receptors and/or an improved perfusion of ventilating lung and working muscles (11) and a reduced activation of ergoreceptors (7) may account for an improved control drive to ventilation.

In summary, this study provides the novel information that exercise training facilitates gas transfer across the alveolar-capillary membrane. Lung function benefits from exercise-training programs and, possibly, contributes to the improvement in exercise performance and ventilatory efficiency.

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REFERENCES