IMPROVEMENT OF ALVEOLAR-CAPILLARY MEMBRANE DIFFUSING CAPACITY WITH EXERCISE TRAINING IN CHRONIC HEART FAILURE

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Running head. Exercise training and pulmonary gas diffusion in heart failure

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ABSTRACT

Chronic heart failure (CHF) may impair pulmonary gas diffusing capacity, an effect that contributes to exercise limitation. We sought to investigate whether improvement of diffusing ability is one of the mechanisms whereby physical training increases aerobic efficiency in this disease. 16 CHF patients were trained (40-min stationary braked cycling, 4 times/week) for 8 weeks; 15 sedentary similar patients were followed-up as controls.

Training increased lung diffusion (DLco+25%), alveolar-capillary conductance (Dm+15%), pulmonary capillary blood volume (Vc+10%), peak exercise O2 uptake (peak VO2+13%), VO2 at anaerobic threshold (VO2 AT+20%), and decreased the slope of exercise ventilation to CO2 output (VE/VCO2-14%). Training also improved the flow-mediated brachial artery dilation (BAD: from 4.8±0.4 to 8.2±0.4%). All these changes were significant compared with baseline and controls.

Hemodynamics were obtained in the last 10 patients enrolled in each group. Training did not affect hemodynamics at rest, and enhanced the increase of cardiac output (+226% vs +187%) and stroke volume (+59% vs +49%) and the decrease of pulmonary arteriolar resistance (-28% vs -13%), at peak exercise. Hemodynamics were unchanged in controls after 8 weeks. Variations with training in DLco and Dm correlated with those in peak VO2 (r=0.64, p =0.007 and r= 0.51, p=0.04, respectively) and with those in BAD (r=0.78, p<0.001 and r=0.50, p=0.04, respectively). After detraining (8 weeks), DLco, Dm, Vc, peak VO2, VO2 AT, VE/VCO2 slope, cardiac output, stroke volume, pulmonary arteriolar resistance at peak exercise and BAD reverted to levels similar to baseline and to those in controls. Our results document, for the first time, that exercise training improves the alveolar-capillary membrane diffusing capacity in CHF, and support the possibility that this effect may contribute to the enhancement of exercise performance.

Key words: Exercise Training, Heart Failure, Alveolar-Capillary Membrane Diffusion.
INTRODUCTION

In chronic heart failure (CHF), ventilation inefficiency, as indicated by the increased slope of the ratio of ventilation to carbon dioxide output (VE/VCO₂ slope) (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 the following: ventilation/perfusion 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), 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 relationship 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). In spite of this, in the interpretation of normalization of the slope relating ventilation to CO₂ output and of decrease in the perceived sense of dyspnea that occurs with physical training, an improvement in lung diffusing capacity has so far been neglected. This, however, does not seem to be an unrealistic possibility, based on the fact that in CHF training produces a systemic amelioration in endothelial function (23,24), that involves the pulmonary vessels (20). In fact, paracrine agents released by the endothelium participate in the control of pulmonary vessel tone and permeability and of the resistance to oxygen 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 increase exercise performance.

METHODS

Study Population. Thirty-eight men, aged 65 years or younger, with compensated CHF due to left ventricular dysfunction (average left ventricular ejection fraction: 35±4%), were randomized to the exercise training group (n=20), or the control group (n=18). Two patients in the trained group and 2 in the control group were excluded because of instability in exercise tolerance in the pre-study interval; 2 patients in the trained group and 1 in the control group were withdrawn 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, University of Milano. 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 NYHA class II or III, a left ventricular ejection fraction at rest of 40% or less, as assessed by echocardiography, no change in drug treatment in the 4 weeks preceding randomization and abstinence from tobacco products for at least 9 months before enrolment. Twelve participants had never smoked. Patients were not recruited if they had had myocardial infarction in the previous 6 months, if they had significant valvular heart disease, hypertension, diabetes mellitus, hypercolesterolemia, pulmonary disease, atrial fibrillation, angina pectoris at rest or on exercise, peripheral vascular disease, musculoskeletal abnormalities precluding exercise training, they were taking lipid lowering agents or antioxidant vitamins, or they currently participated into 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 Figure 1. There were a 4-week pre-study interval and a 16-week study period. The pre-study 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 at the end (test # 2) of this period. Soon after completion of exercise 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 blind to the patient’s assignment. The second exercise test was preceded by an evaluation of the brachial artery endothelial function and of the pulmonary function, in that order, with at least a 60-min interval between one test and the other. The same procedures were repeated at 8 (test # 3) and at 16 weeks (test # 4), in both the trained and the untrained group. The last 10 patients in both groups underwent hemodynamic monitoring during exercise testing # 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 weeks for assessment of compliance (records were taken by the supervisor cardiologist of the patients’ attendance, of duration of the warm-up, aerobic and cool-down phases, and of 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 minutes; during each session, patients completed a 5-minute warm-up phase, a 30-minute aerobic phase and a 5-minute cool-down phase; patients attended the exercise training program 4 times per week. According to the heart rate reserve method (1), exercise intensity was set at 60% for the first 2 weeks and then it was increased, as tolerated, to as high as 80%. All sessions were held at the hospital gymnasium under cardiological supervision. The duration of the training period was 8 weeks, after which patients were asked to avoid exercise (detraining) for further 8 weeks, during which they attended the outpatient clinic every 2 weeks for assessing cardiac symptoms and inquiring 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 minutes of unloaded cycling at 60 rpm followed by a progressively increasing WR exercise and 3 minutes of recovery. Heart rate (HR), 12-lead ECG, and cuff blood pressure were monitored and recorded.

Minute ventilation (VE, BTPS), O₂ uptake (VO₂, STPD), CO₂ output (VCO₂, STPD), and other exercise variables were computer-calculated breath-by-breath, interpolated second by second and averaged 10-second interval (35).

Ventilatory efficiency was assessed by calculating the slope of increase in VE with respect to CO₂ output. The VE/VCO₂ slope was measured by linear regression, excluding the nonlinear part of the data after the onset of ventilatory compensation for metabolic acidosis (32). VO₂ at the anaerobic threshold (AT) and the rate at which VO₂ increased per work rate (ΔVO₂/ΔWR), as an indicator of aerobic efficiency (33), were also measured. ΔVO₂/ΔWR was calculated for the progressively increasing exercise
period, beginning 1 minute after WR started to increase. The delay of 1 minute after the start of increase in WR was used to take into account the time constant for VO$_2$ to respond to the increasing WR (around 35 seconds for normal subjects) (35). Peak VO$_2$ was determined by the highest VO$_2$ achieved during exercise. Age- and weight-adjusted VO$_2$ values were also determined (35). The maximal O$_2$ pulse was measured by dividing the highest VO$_2$ by the simultaneous heart rate. The dead space to tidal volume ratio (VD/VT) was derived by using PaCO$_2$ according to the standard formula (18). The alveolar-arterial difference for O$_2$ pressure (A-aDO$_2$) 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 were obtained that included right atrial, pulmonary artery and wedge pulmonary pressures, cardiac output (thermodilution, in triplicate with these 3 measurements averaged), hemoglobin and plasma protein concentrations. Systemic vascular resistance (SVR) (dynes. sec . cm$^{-5}$) and pulmonary arteriolar resistance (PAR) were calculated as the ratio of mean systemic arterial pressure minus mean right atrial pressure, and, respectively, of mean pulmonary artery pressure minus mean wedge pulmonary pressure, to cardiac output.

At peak exercise, hemodynamic measurements were repeated in an orderly fashion. Blood gases (PaO$_2$, PaCO$_2$) and pH were determined at rest and right 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 assumed a body temperature of 37° C.

**Pulmonary Function.** Spirometry was performed with equipment that met the American Thoracic Society performance criteria (2,21). To adjust for height, age, and sex we used published prediction equations for forced expiratory volume in 1 second (FEV$_1$) and forced vital capacity (FVC) (21). Diffusing lung capacity for carbon monoxide (DLco) was determined twice with washout intervals of at least 4 minutes (the average was taken as the final result) with a standard single breath technique. The maneuver was performed using a test gas with 0.28% carbon monoxide, 0.30% methane, 21% O$_2$, and the balance made up of nitrogen. DLco subdivisions, i.e., the alveolar-capillary membrane diffusion capacity (D$_{Mh}$) and the capillary pulmonary blood
volume available for gas exchange ($V_C$), 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 ($1/D_M$) and the reactive
resistance due to pulmonary capillary blood ($1/\theta V_c$, where $\theta$ = the rate of reaction of
carbon monoxide with hemoglobin), according to the following equation:

$$1/ DLco = 1/ D_M + 1/ \theta V_c$$

The $1/\theta$ value was determined using the following equation, which assumes that the red
cell membrane has a negligible resistance to gas exchange: $1/\theta = 14.6/Hb \times [0.001 \times
PAO_2 + 0.0134]$, where $Hb$ is the subject's hemoglobin concentration (g/dL) and $PAO_2$
is the alveolar $O_2$ partial pressure. Measuring $DLco$ at different $FiO_2$ (20%, 40%, 60%),
a plot of $1/DLco$ against $1/\theta$ will yield a straight line with a Y-intercept of $1/D_M$ and a
gradient of $1/V_c$. The single-breath alveolar volume ($VA$) was derived by methane
dilution. $DLco$, $D_M$ and $V_C$ were expressed in absolute values, as well as per unit of $VA$
($DLco/VA$, $D_M/VA$, $V_C/VA$).

**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 the
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 minutes)
on the forearm. Arterial diameter was measured in millimeters from the artery-blood
interface on both the anterior and posterior wall, coincident with the R waves on the
ECG, for 5 cardiac cycles, with these 5 measurements averaged. Patients were rested
in a supine position for 15 min before the first baseline measurement. After this, the
cuff was inflated for 5 min and then rapidly deflated. A second scan was taken for 90
sec after deflation, with measurements taken 15, 30, 60 and 90 sec following deflation.
Maximal changes were recorded 30 sec after cuff release. After a 10-min rest period, a
further baseline measurement was recorded and 300 µg sublingual nitroglycerin (NTG)
was administered. 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 the Fisher exact test. Univariate 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, the analysis of variance was used to assess a within-group time effect and a student two sample t test was used to assess a group effect with the Bonferroni adjustment. The relationship 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 the Pearson coefficient of correlation. Values are expressed as mean ± SE. Statistical analyses were performed by means of Stata 7.0 software package (Stata Corporation, College Station, TX).

**RESULTS**

Trained and untrained patients had similar baseline characteristics and drug regimen distribution (Table 1). In both groups, forced expiratory volume in 1 sec (FEV1) and vital capacity (FVC) were not consistent with airway obstruction (Table 2); ejection fraction was reduced (Table 3); peak VO2 was compromised and the VE/VCO2 slope was increased exceeding the value of 30 (the upper normal limit) which is typical of CHF patients (3,4,32); the $\Delta$VO2/$\Delta$WR, which reflects the O2 utilized per unit increase in work rate and is an index of aerobic efficiency, was around the lower normal limit of 8.6 (35) (Figure 2). In the study group, DLco and DLco/VA were reduced to $79\pm4\%$ and $77\pm6\%$ of predicted normal values (21) compared to $81\pm5\%$ and $79\pm4\%$ in the control group (Figure 3 and Table 2). Brachial artery flow-mediated vasodilation and NTG-mediated vasodilation were comparable in the two groups (Figure 4). As shown in Table 3, baseline hemodynamic variables, A-aDO2, plasma hemoglobin and protein concentrations, both at rest and at peak exercise, were similar between the groups. Drugs distribution included diuretics, digoxin, a beta-adrenergic receptor blocker and an ACE-inhibitor (Table 1). During the 16-week study, there were minor changes in medications. In the exercise training group, the dose of diuretic was increased in 1 patient and the dose of beta-receptor blocker was reduced in 2 patients, digoxin therapy was discontinued in 1 patient. Among untrained patients, the dose of ACE-
inhibitors was reduced in 2 cases, that of diuretic was increased in 3 cases, and in 2 patients digoxin was withdrawn.

Compared to baseline, at 8-week follow-up, there were no significant changes in any of the examined variables in the untrained group both at rest and during peak exercise (Table 2 and 3; Figures 2, 3, 4). On the contrary, in the trained patients we detected: an increase in DLco (+25%) (in all patients but two), Dm (+15%) (in all patients but one), VC (+10%) (Figure 3), DLco/VA (+25%), Dm/VA (+14%), Vc/VA (+13%) (Table 2), peak VO2 (+13%) VO2AT (+20%), peak O2 pulse (+13%), ∆VO2/∆WR (+15%) (Figure 2), and in flow mediated percent increase in brachial artery diameter (from 4.8 to 8.2%; p<0.01) (Figure 4); a decrease of VE/VCO2 slope (-14%); no changes in VD/VT (Figure 2), FEV1, FVC (Table 2) and in NTG-mediated brachial artery vasodilation (Figure 4).

All the reported changes were significant compared to both the baseline values in these patients and the corresponding values in the untrained group. As to the hemodynamic variables at rest (Table 3), compared with baseline there was a trend towards an increase with training in stroke volume (p=0.092), and towards a decrease in pulmonary arteriolar resistance (p=0.083). Stroke volume was significantly greater (p<0.05), and pulmonary arteriolar resistance significantly lower (p<0.05) when compared with controls (Table 3). At peak exercise, cardiac output and stroke volume were greater, and systemic vascular resistance and pulmonary arteriolar resistance lower with training, compared to both before training and to the corresponding data in the control group. Physical training was also associated with a significant reduction of the A-aDO2 at rest. At peak exercise there was an increase in A-aDO2 in both groups, that, however, was significantly smaller in the trained one (Table 3).

Variations from baseline with training in peak VO2 correlated significantly with those in DLco and Dm (Figure 5, r=0.64, p =0.007 and r= 0.51, p=0.04, respectively), and changes in DLco were related with those in flow-mediated brachial artery vasodilation (Figure 5, r=0.78, p<0.001 and r=0.50, p=0.04, respectively).

At the end of an 8-week detraining interval, values of DLco, Dm, VC, peak VO2, A-aDO2, VO2 AT, VE/VCO2 slope, ∆VO2/∆WR, O2 pulse, cardiac output, stroke volume, systemic and 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.

In no cases there were changes in smoking habit, body weight, 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 (31) in CHF patients, but ventilatory efficiency is impaired. Robin and collaborators (28) first suggested that this might be due to ventilation-perfusion (V/Q) mismatch. In normal subjects, there is some V/Q mismatching due to the effects of gravity (36), which unavoidably results in an A-aDO₂ difference. The difference is small at rest and increases during exercise (9), and this may be related to V/Q mismatch, shunt, or diffusion limitation (6). As a matter of fact, 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 as yet been done on these mechanisms in heart failure.

The present paper reports three major findings. Firstly, in CHF patients exercise substantially increased A-aDO₂, that, as a function of peak VO₂, was greater than in normal individuals (22). Secondly, 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 relationship 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. Thirdly, changes in DLco were associated with a significant reduction in A-aDO₂ at the same workload. It cannot be established whether this reflects also an improvement in exercise-induced hypoxemia, because of lack of measurements of actual in vivo arterial blood temperature. Calculation of O₂ saturation, in fact, is based on measured PaO₂ and changes in body temperature and pH.

What are the mechanisms underlying the improvement in alveolar-capillary membrane conductance? DLco, Dₘ and Vc may have been increasing simply as the consequence of attaining a higher cardiac output plus better diffusion-perfusion matching after training. In fact, since DLco, Dₘ and Vc vary directly with cardiac output, any intervention that increases cardiac output will also secondarily increase DLco, Dₘ and Vc, without implying any intrinsic change of the alveolar-capillary membrane. This would have been better proved if, in addition to those at rest, DLco and cardiac output measurements were performed at the same time at exercise. Lack of these measurements is a basic limitation, which was due to the difficulties that many of these CHF patients had with breath-holding during maximal exercise.
This interpretation, however, would not explain the $D_m$ improvement and A-aDO$_2$ reduction at rest after training, since cardiac output before and after training was unchanged. The gas conductance properties of the alveolar epithelium and capillary endothelium, as well as 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 of transport of Na$^+$ from blood to interstitium. Exercise training was not associated with significant variations in osmotic (plasma protein concentration) and hydrostatic forces (pulmonary artery, pulmonary wedge and right atrial pressures, and ejection fraction). Thus, alternative interpretations for the improved DLco with training may be an increase in $D_m$ properties, or a down-regulation of Na$^+$ and fluid transport from the capillaries to the alveolar interstitial space. The same mechanisms underlying these effects could increase Vc, by producing greater pulmonary vasodilation or better capillary recruitment at any given cardiac output. Under this respect, it is significant that a positive correlation was found between changes in flow-mediated brachial artery dilation and those in DLco and $D_m$, what might suggest that the factors that increase the endothelium-mediated vasodilating properties at the periphery are the same that facilitate O$_2$ diffusion. We can only speculate on the mechanisms linking regular aerobic exercise and pulmonary gas transfer in CHF patients. A possibility is that 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 O$_2$ uptake? 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 O$_2$ consumption (7,11,24,25). However, in this study a positive correlation was found between changes in DLco and those 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-flux 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 to keep alveolar O₂ tension 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 VO₂ and lung diffusion (17,27,30), as well as the acute decrease of peak VO₂ and ventilatory efficiency (steeper VE/VCO₂ slope) after an acute Dm reduction (15). These considerations support the hypothesis that in CHF an impairment in lung diffusion capacity is involved in peak VO₂ 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 VO₂ at anaerobic threshold (delayed reliance on anaerobic pathways for energy production) and in ∆VO₂/∆WR (potentiated aerobic efficiency) indicate a favorable interaction of regular exercise training with more than one mechanism sustaining the increased VE/VCO₂ slope in these patients. A less distended interstitial space and a reduced activation of J- receptors and/or an improved perfusion of both 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.

Acknowledgements

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REFERENCES


LEGENDS FOR FIGURES

Figure 1. Study design.

Figure 2. Oxygen uptake (peak VO₂), oxygen pulse (O₂ pulse), dead space to tidal volume ratio (VD/VT) and changes in oxygen consumption to changes in work rate ratio (ΔVO₂/ΔWR), and VO₂ at the anaerobic threshold (VO₂AT), and slope of the ratio of ventilation to CO₂ production (VE/VCO₂ slope) on exercise, at baseline (week 0), at the end of physical training (8 weeks) and after detraining (16 weeks).

Figure 3. Single values of diffusion capacity for carbon monoxide (DLco), and of its subcomponents the alveolar-capillary membrane conductance (DM) and the pulmonary capillary blood volume (VC), in the trained and the untrained group, at baseline (week 0) at the end of the training period (8 weeks) and after detraining (16 weeks).

* = p < 0.01 for differences from baseline
§ = p < 0.01 for differences from the corresponding value in the untrained group

Figure 4. Flow-mediated and nitroglycerin (NTG)-mediated brachial artery dilatation in the trained and untrained patients at baseline (week 0), at the end of training (8 weeks) and after detraining (16 weeks).

Figure 5. Plot of changes in DLco and DM vs changes in peak VO₂ and of changes in flow-mediated increase in diameter of the brachial artery vs changes in DLco and DM with physical training.
Table 1. Baseline characteristics of the patients who completed the trial.

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<th>UNTRAINED GROUP (n=15)</th>
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<td>Forced expiratory vol. 1 sec, % predicted</td>
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Table 2. Pulmonary Function Data

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<td>3.03±0.49</td>
<td>3.13±0.32</td>
<td>3.18±0.41</td>
<td>3.09±0.27</td>
</tr>
<tr>
<td>DLCO, ml.min⁻¹.mmHg⁻¹.l⁻¹</td>
<td>20.2±4.4</td>
<td>24.4±5.3*§</td>
<td>21.1±3.9</td>
<td>19.9±4.6</td>
<td>20.1±5.2</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>79±4</td>
<td>90±5*§</td>
<td>81±5</td>
<td>81±5</td>
<td>79±7</td>
</tr>
<tr>
<td>DLCO/VA, ml.min⁻¹.mmHg⁻¹.l⁻¹</td>
<td>4.06±0.29</td>
<td>5.09±0.42*§</td>
<td>4.08±0.34</td>
<td>4.31±0.43</td>
<td>4.21±0.58</td>
</tr>
<tr>
<td>DLCO/VA, % predicted</td>
<td>77±6</td>
<td>91±11*§</td>
<td>79±4</td>
<td>79±4</td>
<td>78±7</td>
</tr>
<tr>
<td>DM, ml.min⁻¹.mmHg⁻¹.L⁻¹</td>
<td>31.4±3.2</td>
<td>36.1±3.8*§</td>
<td>31.8±4.1</td>
<td>29.1±3.6</td>
<td>28.8±3.2</td>
</tr>
<tr>
<td>DM/VA, ml.min⁻¹.mmHg⁻¹.L⁻¹</td>
<td>6.07±1.3</td>
<td>6.90±1.6*§</td>
<td>6.10±1.5</td>
<td>5.74±1.2</td>
<td>5.68±1.7</td>
</tr>
<tr>
<td>VC, mL</td>
<td>95±11</td>
<td>105±9*§</td>
<td>96±7</td>
<td>90±8</td>
<td>92±7</td>
</tr>
<tr>
<td>VC/VA, ml.L⁻¹</td>
<td>19.11±2.4</td>
<td>21.52±2.1*§</td>
<td>19.89±2.7</td>
<td>19.53±2.9</td>
<td>19.58±2.1</td>
</tr>
<tr>
<td>VA, L</td>
<td>4.97±0.35</td>
<td>4.99±0.22</td>
<td>5.17±0.24</td>
<td>4.67±0.31</td>
<td>4.77±0.29</td>
</tr>
</tbody>
</table>

Data are means ± 1SD
* = p < 0.01 for differences from baseline
§ = p < 0.01 for differences from the corresponding value in the untrained group

Abbreviations: DLCO = pulmonary diffusion capacity for carbon monoxide; DM = alveolar-capillary membrane diffusion capacity; FEV1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; VA = alveolar volume; VC = pulmonary capillary blood volume
Table 3. Hemodynamics (*), ejection fraction, hemoglobin and plasma protein concentrations, A-aDO2 and body weight

<table>
<thead>
<tr>
<th></th>
<th>TRAINED GROUP</th>
<th></th>
<th>UNTRAINED GROUP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8-week follow-up</td>
<td>16-week follow-up</td>
<td>Baseline</td>
</tr>
<tr>
<td>Measurements at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight, kg</td>
<td>76.4±2.5</td>
<td>75.3±2.3</td>
<td>75.8±2.0</td>
<td>75.2±2.0</td>
</tr>
<tr>
<td>Heart rate, b.min⁻¹</td>
<td>78±12</td>
<td>74±14</td>
<td>79±9</td>
<td>79±15</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>99.6±10</td>
<td>98.3±11</td>
<td>97.8±12</td>
<td>99.3±12</td>
</tr>
<tr>
<td>Cardiac output, L.min⁻¹</td>
<td>4.14±0.6</td>
<td>4.35±0.9</td>
<td>4.08±0.9</td>
<td>4.33±0.4</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>53.1±9.5</td>
<td>58.7±7.8‡</td>
<td>51.6±8.1</td>
<td>55.0±8.4</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>27.2±4.5</td>
<td>25.4±3.9</td>
<td>26.8±4.4</td>
<td>28.3±5.1</td>
</tr>
<tr>
<td>Mean pulmonary wedge pressure, mmHg</td>
<td>20.4±2.2</td>
<td>18.5±2.3</td>
<td>20.2±2.8</td>
<td>19.9±1.8</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes.sec.cm⁻⁵</td>
<td>1835±137</td>
<td>1734±152</td>
<td>1827±161</td>
<td>1760±183</td>
</tr>
<tr>
<td>Pulmonary arteriolar resistance, dynes.sec.cm⁻⁵</td>
<td>131.2±23</td>
<td>126.5±13‡</td>
<td>129.2±21</td>
<td>155.0±11</td>
</tr>
<tr>
<td>Hemoglobin concentration, g.dL⁻¹</td>
<td>14.5±0.6</td>
<td>14.4±0.8</td>
<td>14.7±0.6</td>
<td>14.2±0.4</td>
</tr>
<tr>
<td>Plasma protein concentration, g.dL⁻¹</td>
<td>7.0±0.7</td>
<td>6.9±0.5</td>
<td>7.1±0.6</td>
<td>6.9±0.9</td>
</tr>
<tr>
<td>A-aDO2, mmHg</td>
<td>9.3±1.8</td>
<td>5.2±1.3Δ‡</td>
<td>10.1±2.0</td>
<td>9.6±0.9</td>
</tr>
</tbody>
</table>

Measurements at peak exercise

|                              |               |                                  |                 |                                  |                    |                    |
| Heart rate, b.min⁻¹          | 148±19        | 153±16                           | 149±21          | 152±14                           | 148±22             | 155±20            |
| Mean arterial pressure, mmHg | 115.3±17.2    | 118.4±12.9                       | 116.7±16.8      | 118.2±22.1                       | 119.8±18.7         | 120.7±15.7        |
| Cardiac output, L.min⁻¹      | 11.9±1.7      | 14.20±2.1Δ‡                      | 11.56±1.9       | 12.10±2.2                        | 12.35±2.1          | 12.22±1.8         |
| Stroke volume, mL            | 80.4±15.3     | 92.8±19.6Δ‡                      | 78.6±16.8       | 79.6±17.1                        | 83.4±10.2          | 78.9±17.7         |
| Mean pulmonary artery pressure, mmHg | 45.3±9.1   | 43.1±12.1                        | 44.8±8.2        | 46.9±7.9                         | 47.6±9.3           | 48.2±11.1         |
| Mean pulmonary wedge pressure, mmHg | 28.3±9.9   | 26.9±8.1                         | 27.7±8.8        | 27.1±8.4                         | 26.8±9.2           | 28.5±7.8          |
| Systemic vascular resistance, dynes.sec.cm⁻⁵ | 744.1±118 | 641.1±94Δ‡                       | 776.6±112       | 754.9±129                        | 750.2±96           | 763.8±15          |
| Pulmonary arteriolar resistance, dynes.sec.cm⁻⁵ | 114.2±31.3 | 91.1±22.5Δ‡                      | 117.2±25.6      | 130.7±43.2                       | 134.6±28.3         | 128.9±33.3        |
| Hemoglobin concentration, g.dL⁻¹ | 14.5±0.6  | 14.7±0.5                          | 14.5±0.4        | 14.7±0.5                         | 14.4±0.7           | 14.5±0.6          |
| Plasma protein concentration, g.dL⁻¹ | 6.9±0.9  | 7.1±0.6                          | 7.0±0.7         | 7.1±0.7                          | 6.9±0.8            | 7.0±0.5           |
| A-aDO2, mmHg                 | 29.4±2.5 §    | 17.2±1.6Δ‡ $                      | 27.1±2.1 §      | 29.6±1.2 §                       | 31.8±1.3 §         | 28.1±1.9 §        |

(*) measurements performed in the last 10 patients in both groups. Δ = p < 0.05 for differences from baseline ‡ = p < 0.05 for differences from the corresponding value in the untrained group. §= p<0.05 for differences from the corresponding value at rest. A-aDO2= Alveolar-arterial O2 pressure difference.
Study Design

Run-in

0 weeks 4 weeks 8 weeks 16 weeks

Study Period

Training

Detraining

TRAINED

UNTRAINED

* = RANDOMIZATION

□ = CARDIOPULMONARY EXERCISE TESTING

○ = VASCULAR STUDY

△ = PULMONARY FUNCTION TEST
FLOW-MEDIATED DILATATION

% change in diameter

p<0.01

Trained

Untrained

0 WEEKS  8 WEEKS  16 WEEKS

NTG-MEDIATED DILATATION

% change in diameter

p<0.01

Trained

Untrained

0 WEEKS  8 WEEKS  16 WEEKS