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CARDIORESPIRATORY FUNCTION BEFORE AND AFTER AEROBIC EXERCISE TRAINING IN PATIETNS WITH INTERSTITIAL LUNG DISEASE

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Abstract

PURPOSE—To characterize the cardiorespiratory response to exercise before and after aerobic exercise training in patients with interstitial lung disease (ILD).

METHODS—We performed a clinical study, examining 13 patients (New York Heart Association/World Health Organization Functional Class II or III) before and after 10-weeks of supervised treadmill exercise walking, at 70–80% of heart rate reserve, 30–45 minutes per session, 3 times per week. Outcome variables included measures of cardiorespiratory function during a treadmill cardiopulmonary exercise test (tCPET), with additional near infrared spectroscopy measurements of peripheral oxygen extraction and bioimpedance cardiography measurements of cardiac output. 6-minute walk test distance (6MWD) was also measured.

RESULTS—All subjects participated in at least 24 of their 30, scheduled exercise sessions with no significant adverse events. After training, the mean 6MWD increased by 52±48 meters (P=.001), peak tCPET time increased by 163±130 seconds (P=.001), and time to achieve gas exchange threshold increased by 145±37 seconds (P<.001). Despite a negligible increase in peak oxygen uptake (VO_2) with no changes to cardiac output, the overall work rate/VO_2 relationship was enhanced after training. Muscle oxygen extraction increased by 16% (P=.049) after training.

CONCLUSION—Clinically significant improvements in cardiorespiratory function were observed after aerobic exercise training in this group of subjects with ILD. These improvements appear to have been mediated by increases in the peripheral extraction of oxygen rather than changes in oxygen delivery.

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Key words or phrases

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Over 200 etiologies can result in interstitial lung disease (ILD), which is characterized by irreversible fibrotic reorganization of the lung parenchyma. Interstitial fibrosis creates a barrier to gas exchange at the alveolar-capillary interface, and reduces lung distensibility. As a result, hemoglobin oxygenation is impaired and the work of ventilation is increased, leading to diminished cardiorespiratory function,[1,2] dyspnea,[3,4] and poor exercise performance.[5–7]

In addition to low cardiorespiratory capacity, skeletal muscle weakness has also been associated with poor 6-minute walk test (6MWT) performance in patients with ILD,[8,9] which is the most frequently used method of measuring exercise capacity in these patients.[10–13] For patients with ILD, the minimal clinically important difference (MCID) for distance walked on the test (6MWD) is between 24 and 45 meters[14,13] and a significant decline in 6MWD may warn of impending mortality, particularly in patients with idiopathic pulmonary fibrosis (IPF).[14,15] Although increases in 6MWD beyond the MCID[13,16–21] have been reported after aerobic exercise training (AET) in patients with ILD, the mechanism through which these increases were mediated was not identified.

AET is known to improve cardiorespiratory capacity in individuals who have oxygen (O_2) delivery limitations,[22–27] such as pulmonary arterial hypertension and congestive heart failure. Several studies have previously shown significant increases in 6MWD after AET in patients with ILD[13,16–19,28,29] but only 2 of them attempted to measure cardiorespiratory capacity and only 1[29] of the 2 reported a small but significant increase. Those 2 studies aside, the overall cardiorespiratory adaptation to AET has not been characterized in patients with ILD.

A theoretical framework has been proposed in which AET-induced increases in peak oxygen uptake (VO_2) and cardiorespiratory endurance might be mediated through different pathways.[30–34] Empirical evidence suggests that increases in peak VO_2 may primarily be mediated through increases in central circulatory O_2 delivery, whereas increases in cardiorespiratory endurance appear more likely to be mediated through improved muscle O_2 extraction. The limitation on hemoglobin oxygenation, characteristic of ILD, presents a unique paradigm for study within this framework, where training-induced increases in exercise capacity occur without an improvement in pulmonary respiration.[17,19,35] If so, increases in O_2 delivery may be prevented, even if peak cardiac output and muscle blood flow are improved. Adaptations in cardiorespiratory function would therefore be confined to the periphery and observable only as a function of improved muscle O_2 extraction and its consequences.

We sought to examine this theoretical framework by comparing pulmonary gas exchange, O_2 delivery and O_2 extraction before and after a vigorous AET regimen in patients with ILD. We hypothesized that the cardiorespiratory response to treadmill cardiopulmonary

exercise tests (tCEPT), particularly muscle O_2 extraction capacity, would be improved after training, despite the irreversible limitations to pulmonary gas exchange that generally result from ILD.

METHODS

The institutional review boards of all collaborating authors approved the study prior to subject recruitment for this pre-intervention study. Subjects were recruited specifically for this research program from outpatient clinics in the national capital area between February 2009 and July 2012. After obtaining informed consent, a physician board certified in physical medicine and rehabilitation reviewed subjects' medical histories and charts and performed physical examinations on all subjects to insure meeting of inclusion criteria and the absence of an exclusion criterion. Subjects' most recent pulmonary function tests (PFT), transthoracic Doppler echocardiograms, and right heart catheterizations, typically performed during the past year for routine treatment, were included in the medical history assessment. Subjects with right ventricular systolic pressures ≥40 mmHg, estimated by Doppler echocardiography were further evaluated by right heart catheterization and those with a resting mean pulmonary arterial pressure of ≥25 mmHg were excluded. Subjects with right or left ventricular ejection fractions <40% by echocardiography, significant repolarization abnormalities or arrhythmias identified by resting 12-lead electrocardiogram (ECG) or untoward ECG changes and/or symptoms of ischemia during the baseline tCPET were also excluded. Also patients with forced expired ventilation/forced vital capacity (FEV_1/FVC) ratio <65%, by PFT of participation were not included. The resting ECG, tCPET, and PFT were performed on the first day of participation.

None of the subjects had a history of, or observable, ischemic heart disease, cardiomyopathy or left heart failure, right ventricular failure or *cor pulmonale*, pulmonary hypertension, hepatic or renal failure, metastatic cancer, disabling stroke, or severe psychiatric condition. Patients with uncontrolled diabetes mellitus, musculoskeletal or mitochondrial diseases that would limit tCPET performance, pregnancy, and those on antiretroviral therapy regimens were also excluded. Others excluded were active smokers and those admitting abuse of alcohol or other controlled or illegal substances. None of the subjects had participated in any form of regular AET, for at least 6 months prior to study enrollment.

Measurements

Before and after AET, subjects were weighed with their shoes on and hematocrit was measured from a venous blood sample. Skinfold measures were obtained from the site on the gastrocnemius muscle of the right leg at which light emitters and sensors for near infrared spectroscopy (NIRS) were to be attached. These data were collected because VO_2 measures obtained from tCPET are generally normalized to body weight, and hematocrit and skinfold may influence NIRS muscle oxygenation measurements.

All of the tCPETs, and 6MWT were completed in the Cardiopulmonary and Applied Physiology Laboratory of the Rehabilitation Medicine Department at the NIH Clinical Center in Bethesda, MD. The 6MWT were conducted on an 80-meter circular track, according to the guidelines of the American Thoracic Society.[36] tCPETs were conducted on

a motorized treadmill, with computerized adjustments of belt speed and degree of incline. A modified-Naughton tCPET protocol[27] was used. The target endpoint of the tCPET was the subject's expressed desire to stop the test, despite strong verbal encouragement from the testing staff (volitional exhaustion). Tests were also stopped in the event of intolerable exertional dyspnea.

Pulmonary gas exchange was measured continuously using breath-by-breath open circuit spirometry (MedGraphics, Cardio 2 Ultima, Medical Graphics Corp, St Paul, MN). For subjects regularly using supplemental O_2, medical air (21% O_2 and 79% N_2) was blended with respiratory grade O_2 to raise the fraction of to 40% O_2. The method for this procedure was previously described.[27] The principal outcome measures for the tCPET were VO_2, work rate (WR), gas exchange threshold (GET), time to attain GET (GET-time), and time to volitional exhaustion (tCPET-time). The GET was identified by the V-slope method. Peak VO_2 was determined by an 8-breath average at the end of the test or at the end of the last completed stage, whichever was higher. WR was calculated using body weight, treadmill speed, and % grade of incline during tCPETs. A linear regression model was determined to fit the WR-VO_2 iterations most closely and used to examine the work rate/VO_2 relationship.

Heart rate was measured by ECG, and cardiac output and stroke volume were measured by transthoracic bioimpedance cardiography throughout the tCPET (PhysioFlow PF-05 Lab 1, Manatec Biomedical, France). Muscle O_2 extraction measures included peak arteriovenous O_2 difference (a-vO_2) and muscle oxygenation indices, which were obtained by continuous wave near-infrared spectroscopy (NIRS; Oxymon MK-III, Artinis Medical Systems, The Netherlands). The a-vO_2 was calculated as the quotient of VO_2 and cardiac output. Muscle oxygenation was measured in the gastrocnemius muscle of the right leg and included amplitude changes in concentrations of deoxygenated ([deoxy-Hb/Mb]) and oxygenated ([oxy-Hb/Mb]) hemoglobin/myoglobin from rest to volitional exhaustion during tCPET. Total tissue hemoglobin ([tot-Hb/Mb]) concentration was calculated as the sum of [oxy-Hb/Mb] and [deoxy-Hb/Mb] whereas the hemoglobin concentration difference ([diff-Hb/Mb]) was determined by subtracting [deoxy-Hb/Mb] from [oxy-Hb/Mb].

Aerobic Exercise Training Regimen

AET comprised a 10-week, professionally supervised, program of treadmill walking for 30–45 minutes per session, 3 times per week in an outpatient pulmonary rehabilitation center. Completion of 24 of the 30 training sessions was required to sustain participation in the program. Each session began with a 5–10 minute warm-up not included in the 30–45 training period. The target intensity was 70–80% of subjects' heart rate reserve determined from the initial tCPET.[38] Treadmill speed and grade were continuously adjusted to keep the heart rate as close as possible to the target zone. All subjects requiring supplemental oxygen during training received a flow rate adequate to maintain SpO_2 ≥85%.

Education

Subjects also received an ancillary series of lectures related to their disease process. These lectures were approximately 1 hour in length. They covered anatomy and physiology, lung disease processes, medication use, oxygen therapy, sleep disorders, preventing infection,

airway clearance, interpreting pulmonary function tests, energy conservation, panic control, relaxation techniques, breathing retraining, community resources, advance directives, social well-being, nutrition, and benefits of exercise.

Statistical Analysis

Differences between the pre- and post-AET outcome measures were analyzed using one-tailed paired *t*-tests. A Related-Samples Wilcoxon Signed Rank Test was used for data that did not meet statistical assumptions of normalcy. Use of the 1-tailed analyses was justified by meeting both of the required underlying assumptions: 1) plausibility was substantiated in the background information that our results would be directional,[18,29] and 2) our directional hypothesis was proposed prior to the analysis. Use of the 1-tailed analysis increased the statistical power of the study and minimized the probability of type-2 error while maintaining our *a priori* alpha level of 0.05. The significance of relationships between the independent variables was assessed by Pearson product moment correlation coefficients or Spearman ranked coefficients if the data did not meet the assumptions of normalcy. *P*-values ≤.05 were considered statistically significant. All statistical analyses were conducted using SPSS version 21 (IBM, Inc.). Data are presented as mean±1 standard deviation.

RESULTS

Thirteen patients with New York Heart Association/World Health Organization (NYHA/WHO) Class II or III ILD (Table 1) were studied. 69% of the patients required supplemental O_2. At baseline, total lung capacity was 57.0 ± 17.5%, FVC was 52.9 ±18.0%, and lung diffusion (DLCO, available in 12 of 13 subjects) was 39.4 ± 15.0% of predicted values. While FEV_1 was only 57.0 + 23.3% of predicted values, the FEV_1/FVC ratio was 83.4 ± 3.6% of predicted. Subjects were deconditioned as indicated by an attained peak VO_2 of only 73 ± 32% of the predicted values for sedentary normal individuals of similar age and gender at baseline. However, when considering only patients that performed the tCPET without supplemental oxygen, this percentage was much lower (61 ± 22 %). Diminished resting cardiac output was not apparent in these subjects but a slight resting tachycardia with a normal stroke volume was observed at baseline (Table 3). Neither cardiac output nor stoke volume appeared to be diminished at peak exercise. End-tidal partial pressure of oxygen ($PETO_2$) and end-tidal partial pressure of carbon dioxide $PETCO_2$ were substantially higher than expected at rest as well as at peak exercise. Arteriovenous O_2 difference was slightly higher than expected at rest and was severely diminished at peak exercise. Results of the baseline pulmonary and cardiorespiratory assessments were consistent with a restrictive breathing pattern accompanied by normal central circulatory O_2 delivery, impaired pulmonary gas exchange, and diminished muscle O_2 extraction capacity.

Subjects participated in 90% (Table 2) of the training sessions without a serious adverse event. Five subjects spent less than 70% of the targeted 30–45 minutes in their training heart rate zone, while eight subjects spent 70% or more of the time in the training zone (Table 2). No significant changes in subjects' body weight (81.5 ± 16.4 vs. 81.1 ± 17.1 kg, *P*=.200), gastrocnemius skin fold (23 ± 11 vs. 21 ± 11 mm, *P*=.239), or hematocrit (40.5 ± 2.8% vs. 40.7 ± 3.0%) were observed over the study period.

After training, resting heart rate and cardiac output were significantly reduced but still uncompromised (Table 3). While a significant increase in peak cardiac output, and stroke volume were not observed, peak a-vO_2 was significantly higher after training. Additionally, [deoxy-Hb/Mb] and [diff-Hb/Mb] amplitudes were increased without a significant increase in [tot-Hb/Mb] after training (Figure 3) and the increases in a-vO_2 and [deoxy-Hb/Mb] correlated significantly (r=0.511; *P*=.045). Increases of 12% (~52 meters) in 6MWD and 32% (~39 watts) in peak WR were observed after AET. Significant increases in GET-time and tCPET-time were also observed (Figure 1). A statistically significant increase in peak VO_2 was observed after training but this increase was too small to be of clinical relevance.[39] Conversely, WR was higher at any given level of VO_2 after AET (Figure 2).

DISCUSSION

The cardiorespiratory adaptation to vigorous AET was characterized in patients with ILD. The cardiorespiratory response to tCEPT, particularly muscle O_2 extraction, was improved after AET. Before AET, cardiorespiratory capacity was found to be limited by diminished muscle O_2 extraction, as well as the pulmonary consequences of ILD. A significant increase in muscle O_2 extraction was observed after AET without an increase in either central O_2 delivery or muscle O_2 availability. We therefore suspect that the increase in O_2 extraction may have resulted from improved mitochondrial function. Concomitant with the increase in muscle O_2 extraction, was an improvement in cardiorespiratory endurance, as measured by 6MWD, peak WR, GET-time, and tCPET-time. Together, these findings lend support to a more general construct suggesting that cardiorespiratory endurance may be mediated primarily through improved muscle O_2 extraction rather than by increases in cardiac output or peak VO_2.

The overall pattern of adaptation observed in this study was different than expected. Resulting from increases in both central circulatory O_2 delivery to the muscles and muscle O_2 extraction,[39] peak VO_2 is generally expected to increase by 12% to 21%, in healthy normal subjects, following AET.[40] At submaximal work rates, VO_2 tends to remain similar in the pre- and post-training conditions.[31] Therefore, any given level of submaximal work becomes more economical in a post-training state because the work is sustained at a lower percentage of maximum cardiorespiratory capacity.[31] Conversely, peak VO_2 increased by only 4.4% in these patients with ILD. This was similar in magnitude to that observed in a previous report (6.2%)[29] but its clinical relevance could not be determined.[26,27,39–42] Patients in the current study adapted to AET primarily through a mechanism that permitted a higher work rate to be achieved at any given VO_2, while prolonging the occurrence of the anaerobic threshold and the attainment of peak VO_2. While, peak VO_2 may be influenced by non-physiological factors such as motivation, the leftward shift in the WR-VO_2 slope and increased GET-time are markers that are not affected by nonphysiological influences.

O_2 delivery to the tissues is dependent on adequate oxygenation of hemoglobin at the alveoli. In ILD, the irreversible fibrotic parenchyma creates a diffusion barrier that impedes hemoglobin oxygenation. A restricted ventilatory pattern can exacerbate the impediment by creating alveolar hypoxia, decreasing ventilation to perfusion ratio, and increasing the work of breathing. In the current study, peak cardiac output, stroke volume and heart rate did not

increase after AET in patients with ILD. However, a 16% improvement in peak a-vO_2, as well as a significant increase in unloading of O_2 from the hemoglobin in the muscle microvasculature, was observed after training. Thus, the observed improvements in cardiorespiratory function appeared to be mediated only by increased muscle O_2 extraction capacity.

Clinical Implications

In the current study, the increase in 6MWD after AET exceeded the increases observed in most of the previous studies,[13,16–20,28] as well as the current ILD-specific MCID estimates.[14,13] The training regimen used in this study was more vigorous than those used in previous studies yet high levels of participation were observed without any significant adverse events. After training a given work rate was met by a lower VO_2, thus reducing multisystemic stress at any given, intensity of activity. Moreover, the post-training increase in muscle O_2 extraction did not adversely affect SpO_2 during exercise. The current study demonstrated that even very vigorous aerobic exercise training might be safe, quite well tolerated, and beneficial for improving muscle O_2 extraction, work rate to VO_2 ratio, and overall exercise and physical activity performance in patients with ILD.

Study Limitations

First, the small sample size and absence of a non-training control group preclude the ability to generalize our results. Further validation of the findings in a larger, broader group of patients with ILD is required. Despite this, a significant cardiorespiratory adaptation to aerobic exercise training was observed in the subjects of this study. For variables not achieving statistical significance, the numerical differences in pre- versus post-training scores were typically small and generally did not trend toward a clinically important improvement.

Second, the clinical course of ILD often includes a rapid decline in systemic function that could further diminish cardiorespiratory capacity over a short period of time. If so, the effect of training may have been underestimated in this study. Alternatively, the rapid decline in systemic function in ILD could potentially preclude acquiring the physiologic benefits of exercise training noted in this study, particularly at later stages of the disease. It should also be recognized that patients with ILD and pulmonary hypertension, who were excluded from this study, may adapt differently to aerobic exercise training.

Third, 6MWD is a performance measure that, like volitional exhaustion, can be influenced by acclimation. We could not account for the influence of possible Hawthorne or practice effects. However, no significant increases in 6MWD were observed for non-exercise training control groups in previous studies.[17,18]

Lastly, the sample was heterogeneous with respect to inclusion of patients with various ILD etiologies. The size of the sample was insufficient for subgroup analyses based on etiology. This again may impede the ability to generalize information over the entire ILD classification. However, a degree of homogeneity in the sample was established because a restrictive breathing pattern, impaired gas exchange, and poor exercise performance, all of

which are cardinal manifestations of all ILD etiologies, were present in each of the subjects included.

CONCLUSION

Patients in this study adapted to aerobic exercise training through a mechanism that increased cardiorespiratory endurance. Muscle O_2 extraction was enhanced in the post-training condition, without a change in cardiopulmonary O_2 delivery or muscle O_2 availability. From a clinical perspective, the results of this study provide evidence that exercise training of even vigorous intensities may be safe and well tolerated by patients with ILD and that participation in aerobic exercise may improve muscle O_2 extraction, and exercise performance in these patients.

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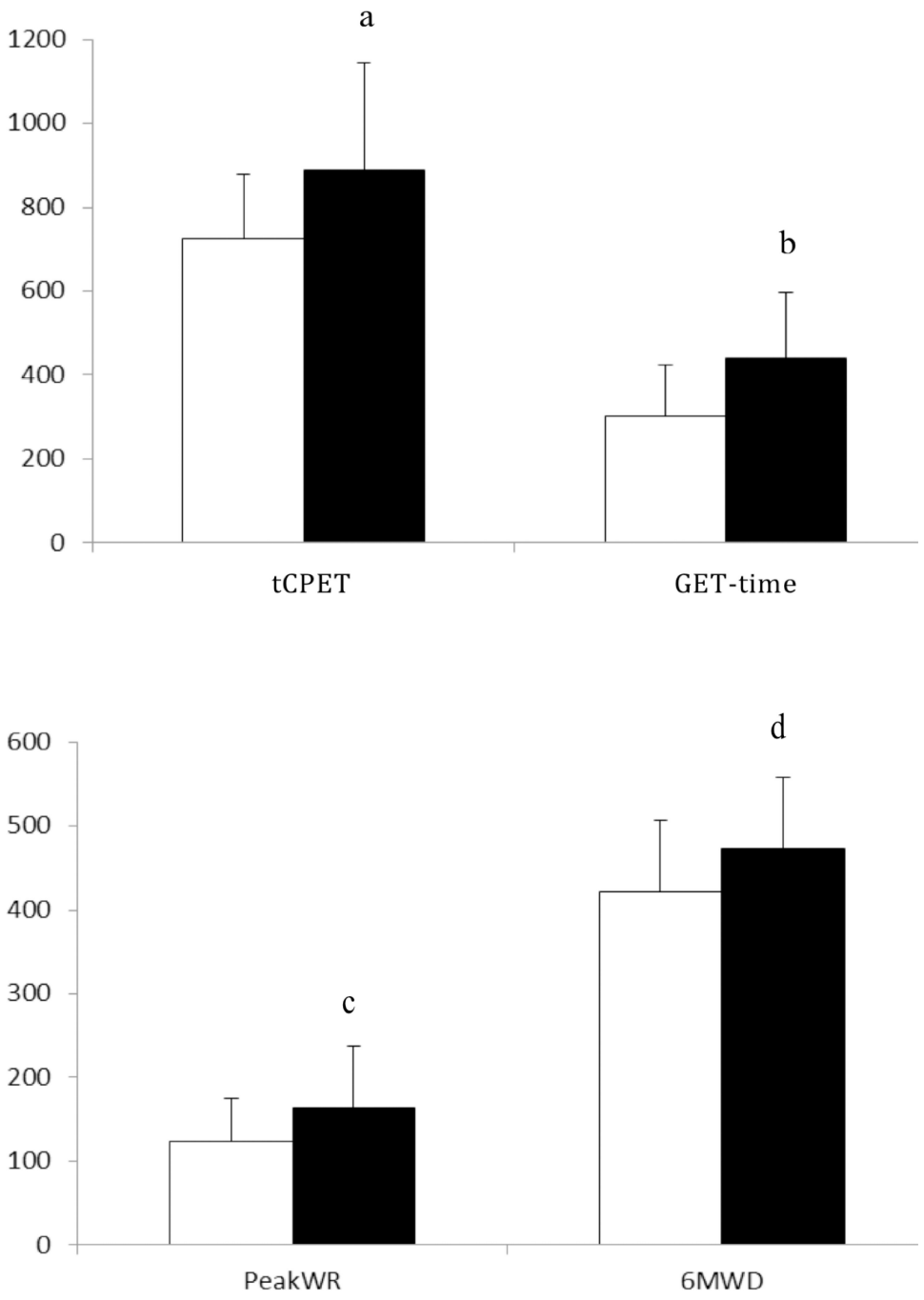

Figure 1.

Test duration (tCPET), time to gas exchange threshold (GET-time), peak work rate (WR) and 6-minute walk test distance (6MWD) in the untrained (white bars) and trained (black bars) patients with ILD. Error bars equal 1 standard deviation unit.

[a]tCPET was 163±130 seconds longer in the trained than in the untrained state (*P*=.001).

[b]GET-time was 145±15 seconds longer in the trained than in the untrained state (*P*<.001).

[c]Peak work rate (WR) was 43±37 watts greater (*P*=.002).

[d]6MWD was 52±48 meters farther in the trained versus the untrained state (*P*=.001)

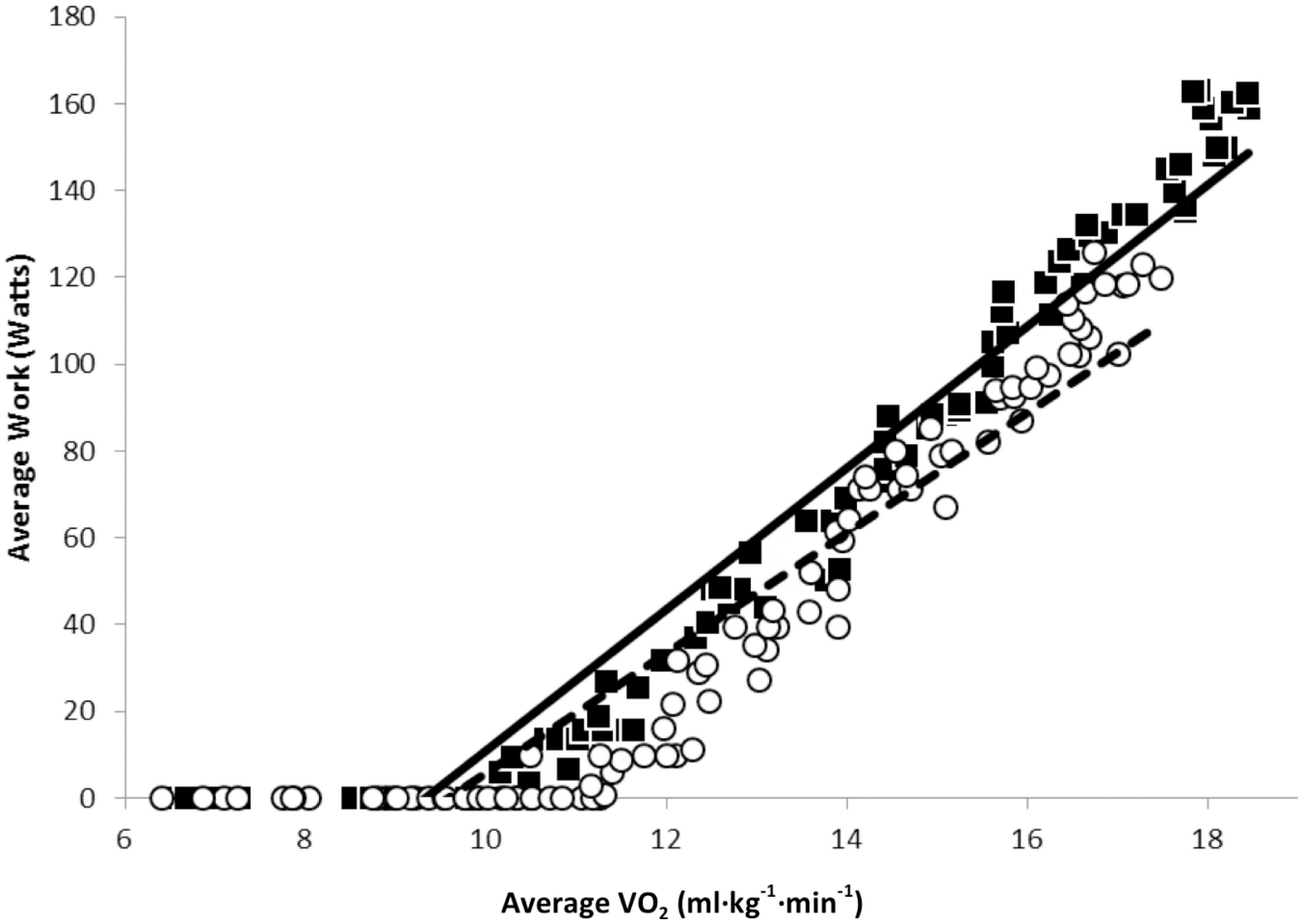

Figure 2.

Work rate-oxygen uptake (VO_2) slope in the untrained (white circles) and trained (black squares) conditions. Regression equation was y=13.838x−132.54; R2 = 08813 for the untrained condition (dotted line) and y=16.274x−151.86; R2=09343 for the trained (solid line) condition. Slope was significantly higher (*P*=.002) in the trained (14.89±4.94) than in the untrained (11.86±4.87) condition.

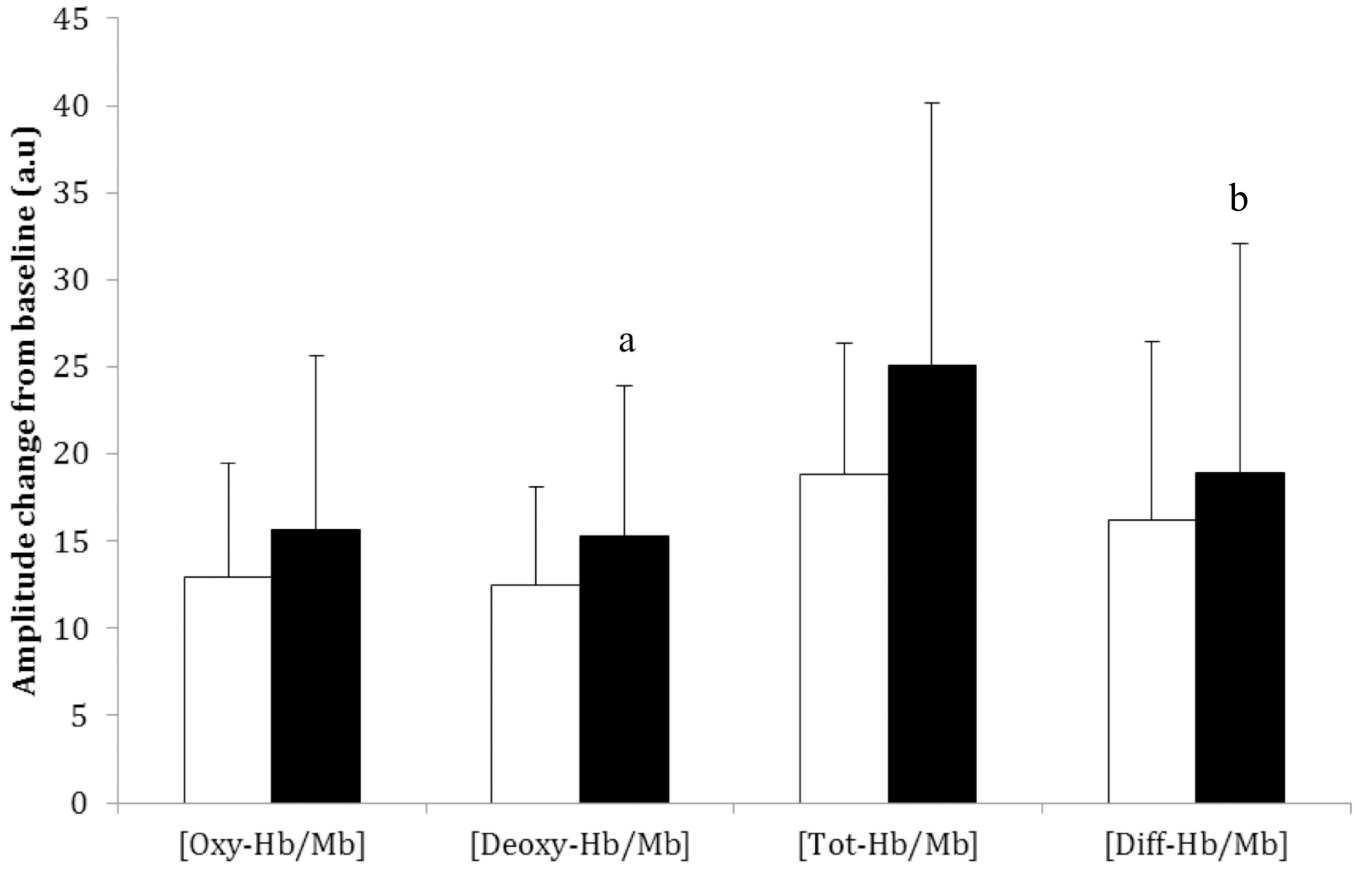

Figure 3.

Muscle oxygenation capacity in the untrained and trained conditions. Bars represent concentration changes for oxygenated ([oxy-Hb/Mb]), deoxygenated ([deoxy-Hb/Mb]), total ([Tot-Hb/Mb]), and difference (diff-Hb/Mb) in hemoglobin/myoglobin. White bars represent the untrained condition and black bars represent the trained condition. Error bars represent 1 standard deviation unit.

[a][deoxy-Hb/Mb] was significantly greater in the trained versus the untrained state (*P*=.037).

[b][diff-Hb/Mb] was significantly greater in the trained versus the untrained state (*P*=.027).

Table 1

Baseline Characteristics of Study Patients

Characteristics	All Patients (n=13)
Age, y, mean (SD)	57.0 (9.1)
Female, n (%)	9 (69)
Race/ethnicity, n (%)	
White	11 (85)
African American	2 (15)
BMI, kg/m^2, mean (SD)	28.6 (4.8)
Supplemental O_2 use, n (%)	5 (38)
Diagnosis, n (%)	
Nonspecific interstitial pneumonitis	6 (46)
Idiopathic pulmonary fibrosis	3 (23)
Systemic sclerosis	2 (15)
Desquamative interstitial pneumonia	1 (8)
Sjögren's syndrome	1 (8)
NYHA/WHO Functional Classification, n (%)	
Class II	6 (46)
Class III	7 (54)

Abbreviations: BMI, body mass index; NYHA/WHO, New York Heart Association/World Health Organization

Table 2

Aerobic Exercise Training Summary of Subjects Completing a Minimum of 24 Sessions

Subject	Total Sessions	Total Exercise Time (min)	Time in Training Zone (% of total exercise time)	Average HR (% HRR)	Supplemental Oxygen Use (L/min)
1	25	943	97	72	-
2	30	1159	97	71	6
3	27	1065	44	68	6
4	26	1020	73	70	6–15
5	25	976	85	72	-
6	25	975	96	71	3–6
7	28	1074	68	70	10–15
8	25	975	44	68	2–4
9	27	1027	11	67	6–15
10	27	1065	89	71	-
11	29	1036	82	70	-
12	28	1095	92	72	3–5
13	26	1042	38	69	2–12
Mean	27	1035	70	70	7
SD	1.6	59.0	27.7	1.7	1.5

Abbreviations: HRR, heart rate reserve

Table 3

Cardiorespiratory Measures

Outcome Measures	Pre-training	Post-training	Difference	*P* value
Resting				
VO_2, mL·kg^{-1}·min^{-1}	5.4 (2.4)	5.2 (2.3)	− 0.2	.384
VCO_2, mL·kg^{-1}·min^{-1}	4.3 (1.3)	4.0 (1.6)	− 0.3	.234
f, breaths/min	31 (8.4)	31 (9.5)	0	.463
Ve, l/min	15.3 (4.0)	14.7 (5.2)	− 0.6	.323
Vt, ml/min	2.1 (0.6)	2.3 (0.8)	+ 0.2	.172
RER	0.88 (0.21)	0.80 (0.23)	− 0.08	.463
a-vO_2, vol%	6.1 (2.7)	6.6 (2.8)	+ 0.5	.091
$PETO_2$, mmHg	154.8 (61.7)	149.4 (54.6)	− 5.4	.197
$PETCO_2$, mmHg	38.0 (5.7)	38.9 (6.7)	+ 0.9	.125
Heart rate, beats/min	103 (13.1)	95 (11.3)	− 8	.024
Cardiac stroke volume, ml	72.0 (13.8)	67.9 (16.0)	− 4.1	.136
Cardiac output, l/min	7.3 (1.7)	6.4 (1.6)	− 0.9	.027
Peak				
VO_2, mL·kg^{-1}·min^{-1}	17.4 (5.5)	18.2 (5.0)	+ 0.8	.048
VCO_2, mL·kg^{-1}·min^{-1}	19.5 (4.7)	19.8 (4.7)	+ 0.3	.293
f, breaths/min	53 (11.0)	52 (9.3)	− 1	.359
Ve, l/min	55.1 (15.13)	54.0 (16.1)	− 1.1	.192
Vt, ml/min	1029 (361.2)	1055 (419.4)	+ 26	.242
RER	1.17 (0.23)	1.11 (0.17)	− 0.06	.037
a-vO_2 difference, %	9.2 (2.2)	10.7 (2.9)	+ 1.5	.049[a]
$PETO_2$, mmHg	160 (58.4)	158 (56.1)	− 2	.08[a]
$PETCO_2$, mmHg	41 (9.6)	43 (9.7)	+ 2	.055
Heart rate, beats/min	148 (18.0)	144 (14.2)	− 4	.086
Cardiac stroke volume, ml	105 (20.1)	99 (21.8)	− 6	.179
Cardiac output, l/min	15.7 (3.8)	14.5 (4.0)	− 1.2	.177

[a]Wilcoxon Signed Ranks Test.

Abbreviations: tCPET, treadmill cardiopulmonary exercise test; VO_2, minute oxygen uptake; VCO_2, minute carbon dioxide expiration; *f*, breathing frequency; Ve, minute ventilation; Vt, tidal volume; RER, respiratory exchange ratio; a-vO_2, arteriovenous oxygen difference; $PETO_2$, end-tidal partial pressure of oxygen; $PETCO_2$, end-tidal partial pressure of carbon dioxide.