Cardiopulmonary Rehabilitation Enhances Heart Rate Recovery in Patients With COPD

Vasiliki V Georgiopoulou MD, Stavros Dimopoulos MD, Dimitrios Sakellariou MD, Ourania Papazachou MD, Vasiliki Gerovasili MD, Athanasios Tasoulis MD, Varvara Agapitou MD, Ioannis Vogiatzis MD, Charis Roussos MD, and Serafim Nanas MD

BACKGROUND: Autonomic dysfunction is present early in the course of COPD, and is associated with adverse outcomes. We utilized heart rate recovery, a simple and validated index of autonomic balance, to investigate the effects of exercise training on autonomic dysfunction in patients with COPD. METHODS: We evaluated 45 stable subjects with COPD who participated in a 36-session exercise-based cardiopulmonary rehabilitation program. Subjects underwent maximal cardiopulmonary exercise testing at baseline and after completion of the rehabilitation program. We recorded exercise testing parameters and heart rate during rest, exercise, and recovery. Heart rate recovery was calculated as heart rate at peak exercise minus heart rate at the first minute of recovery. RESULTS: Thirty-nine subjects (age 66.3 ± 7.8 y, 90% male, body mass index 27.1 ± 4.1 kg/m^2, FEV_1 45.7 ± 18.7%) completed the program. In these subjects, heart rate recovery increased from 16.2 ± 8.0 beats/min to 18.4 ± 8.4 beats/min ($P = .01$), resting heart rate decreased from 88.0 ± 10.7 beats/min to 83.3 ± 10.5 beats/min ($P = .004$), and heart rate at anaerobic threshold decreased from 109.0 ± 12.5 beats/min to 105.5 ± 11.7 beats/min ($P = .040$). In addition, oxygen consumption ($\dot{V}_{O_2}$) increased from 14.3 ± 3.7 mL/kg/min to 15.2 ± 3.8 mL/kg/min at peak exercise, and from 9.7 ± 2.4 mL/kg/min to 10.4 ± 2.6 mL/kg/min at anaerobic threshold (both $P = .02$), while the $\dot{V}_{O_2}$/t slope increased from –0.32 ± 0.16 mL/kg/min^2 to –0.38 ± 0.19 mL/kg/min^2 ($P = .003$). Parameters of ventilatory performance improved also. CONCLUSIONS: In subjects with COPD, exercise-based rehabilitation improves heart rate recovery, modestly though, which indicates a degree of attenuated autonomic dysfunction. Exercise and muscular oxidative capacity, as expressed by $\dot{V}_{O_2}$/t slope, is also improved. *Key words: autonomic nervous system; ergometry/exercise test; heart rate; COPD; rehabilitation/exercise therapy.* [Respir Care 2012;57(12):2095–2103. © 2012 Daedalus Enterprises]

Introduction

Several studies have demonstrated the strong association between autonomic nervous system dysfunction and increased mortality in a variety of diseases.[1] Autonomic dysfunction is present in the early stages of COPD.[2] Although the exact nature of the alterations is still debated,[3,4] the existing data point clearly to a disrupted sympathovagal balance. From a clinical standpoint, autonomic dysfunction is associated with adverse outcomes in patients with COPD.[5]

The authors are affiliated with the Cardiopulmonary Exercise Testing and Rehabilitation Laboratory, First Critical Care Medicine Department, Evgenidio Hospital, National and Kapodistrian University of Athens, Greece. Dr Georgiopoulou is also affiliated with Emory Clinical Cardiovascular Research Institute, Emory University, Atlanta, Georgia.

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Correspondence: Serafim Nanas MD, Cardiopulmonary Exercise Testing and Rehabilitation Laboratory, First Critical Care Medicine Department, Evgenidio Hospital, National and Kapodistrian University of Athens, Greece, 20 Papadiamantopoulou Street, Athens, 11528, Greece. E-mail: a-icu@med.uoa.gr.

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Exercise training exerts a beneficial effect on sympathovagal balance. This effect has been demonstrated in patients with heart failure, post myocardial infarction, diabetes mellitus, and in asymptomatic elderly individuals.[6,7] In fact, this favorable response has led to reduced mortality in certain populations.[1,8] In patients with COPD, pulmonary rehabilitation programs as a multidisciplinary intervention therapy have been shown to improve symptoms, exercise capacity, and quality of life.[9,10] In addition, the number of hospitalizations and stay related to respiratory disease are reduced.[11,12] However, the effect of exercise training on autonomic dysfunction in patients with COPD has not been fully investigated.

Among the various validated indicators of autonomic dysfunction, heart rate recovery is probably the most practical, inexpensive, and widely accessible.[13] Heart rate recovery correlates with heart rate variability at rest and/or during the early recovery phase.[14,15] Importantly, heart rate recovery has been shown to entail independent prognostic information in several clinical settings, including asymptomatic adults,[16] diabetes mellitus,[17] post myocardial infarction,[18] heart failure,[19] and COPD.[5] The purpose of our study was to investigate the effects of an exercised-based cardiopulmonary rehabilitation program on the sympathovagal balance of patients with COPD, as expressed by the response of heart rate during recovery after maximal exercise testing.

QUICK LOOK

Current knowledge

There is a strong association between autonomic nervous system dysfunction and increased mortality in patients with COPD. Autonomic dysfunction is present in the early stages of COPD and can be attributed to disrupted sympathovagal balance.

What this paper contributes to our knowledge

In patients with COPD, exercise-based rehabilitation improves heart rate recovery, modestly though, which indicates a degree of attenuated autonomic dysfunction. Exercise and muscular oxidative capacity, as expressed by oxygen consumption/time slope, is also improved.

Methods

Study Subjects

We recruited 45 clinically stable patients (age 66.5 ± 7.6 y, 40 male, body mass index 27.3 ± 4.3 kg/m^2) with stage II–IV COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.[20] All subjects were receiving optimal medical treatment, including inhaled β_2 agonists, anticholinergic, corticosteroid, and oral theophylline agents. Patients entered the study if stable on medical treatment for ≥ 6 weeks. Patients with atrial fibrillation, coronary artery disease, substantial valvular disease, heart failure, or diabetes were excluded. We also excluded patients receiving digoxin, β blockers, nondihydropyridine calcium channel blockers, or other rate-modulating medications, as well as patients with permanent pacemakers or implantable defibrillators. All subjects were former smokers and had not experienced a respiratory-tract infection or exacerbation for at least 6–8 weeks before the study. The institutional ethics committee approved the study. All participants were required to give written informed consent prior to exercise testing. There was no financial compensation for participation.

Pulmonary Function Tests

Flow volumes were determined by spirometry, according to American Thoracic Society recommendations.[21] The highest value from 3 properly performed attempts was used for analysis. Values were expressed both as absolute values and as percentage of reference values. Maximum inspiratory pressure was also measured. The recordings were performed using a system for pulmonary and metabolic tests (Vmax 229, SensorMedics, Yorba Linda, California).

During pulmonary function test (PFTs), subjects were sitting and breathing through a scuba-type mouthpiece attached to a 3-way valve with a small leak incorporated into the airway. For maximum inspiratory pressure determination, subjects were instructed to exhale up to the residual volume and then perform the maximal inspiratory effort through the mouthpiece.

Exercise Testing and Rehabilitation Program

In order to minimize the learning curve effect, all participants were familiarized with the test, the laboratory, and all the procedures during an initial run-in period.[22] This allowed for mitigation of possible subject concerns about the test and better understanding of the communication techniques during the test, including hand signs and symptom scoring.[23]

Participants were fasting for at least 4 hours prior to exercise testing, had refrained from alcoholic and caffeinated beverages for at least 12 hours, and had received their regular medications; strenuous physical activity was discouraged for 24 hours before testing. To determine baseline functional capacity, an incremental symptom-limited cardiopulmonary exercise test (CPET) was performed on an electromagnetically braked cycle-ergometer (Ergoline

800, SensorMedics, Yorba Linda, California). Initially, the subjects were required to sit for 2 min to obtain baseline measurements and assume their normal breathing pattern (ie, avoid hyperventilation). Additional time was given if needed based on the slope of the line created by the pulmonary oxygen uptake ($\dot{V}_{O_2}$) values obtained over time and displayed on the screen, which should zero. Heart rate at the end of this period was considered as the resting heart rate for the study. Subsequently, they entered a 3-min warm-up stage of pedaling at 0 watts (60 rpm). Afterwards, the work load increased every minute, according to the equation from Hansen et al,[24] and subjects were encouraged to continue exercising until limited by symptoms (leg fatigue or intolerable dyspnea). Criteria for terminating exercise included symptoms, subject request, signs of myocardial ischemia, tachycardia, severe decline in oxygen saturation, and hypotension. Because different body postures result in different values for heart rate recovery, all subjects remained inactive in the sitting position on the ergometer throughout recovery. All tests were performed at the same time of the day, and the same procedures were strictly followed at the end of the cardiopulmonary rehabilitation program. There were no changes in heart rate-modulating medications among the subjects who completed the program.

Pulmonary gas exchange and ventilation were recorded with calibrated signals from rapidly responding gas analyzers and a mass flow sensor (Vmax 229, SensorMedics, Yorba Linda, California), through a mouthpiece with a nose clip in place. The following variables were recorded breath by breath, using the 20 s average values for $\dot{V}_{O_2}$, pulmonary carbon dioxide output ($\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$), respiratory rate, and the respiratory equivalents for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) and CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$). The maximum work load at which a subject was able to complete 30 s of cycling at 50 rpm was designated as the maximum work capacity. The $\dot{V}_{O_2}$-peak was defined as the maximum value of $\dot{V}_{O_2}$ during the last 20 s of exercise, and $\dot{V}_{O_2}$ at anaerobic threshold was estimated by the V-slope method. In addition, we used the respiratory exchange ratio to confirm increased $\dot{V}_{CO_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ was calculated as the slope by linear regression of $\dot{V}_E$ versus $\dot{V}_{CO_2}$ from the beginning of exercise to anaerobic threshold, where the relation is linear. The oxidative capacity of muscles was estimated by the first-degree slope of $\dot{V}_{O_2}$ decline during the first minute of recovery ($\dot{V}_{O_2}$/t-slope). This was calculated by linear regression, as described in previous studies.[25–27] We also calculated the time for 50% decline of $\dot{V}_{O_2}$-peak during recovery ($t_{1/2}\dot{V}_{O_2}$-peak) by measuring the time required for a 50% fall in the peak value of $\dot{V}_{O_2}$, as it was previously described. When this occurred in the middle of 2 sampling points, we set $t_{1/2}$ at the second of these points.[27] $\dot{V}_E$, respiratory rate, tidal volume, inspiratory time, expiratory time, and total breathing cycle time were recorded at a standardized work load for each subject (the work load representing the maximum work capacity achieved during CPET before the rehabilitation program). Heart rate and arterial oxygen saturation were monitored continuously. All subjects were on continuous electrocardiographic monitoring and recording. Heart rate and rhythm were monitored by a 12-lead ECG system (Marquette MAX 1, Madison, Wisconsin). The heart rate at the end of the exercise, which was determined as the average over the last 10 seconds of cycling, was considered the maximum heart rate. The heart rate at the first, second, and third minute of recovery was determined as a 5-s average at minute 1, 2, and 3 after the end of exercise. Blood pressure and perceived symptoms were recorded at rest and every 2 min during exercise and recovery.

Heart rate recovery was defined as the difference in heart rate at maximal exercise minus heart rate at the first minute of recovery, while heart rate response from resting to anaerobic threshold was defined as the difference between heart rate at anaerobic threshold minus resting heart rate. We also calculated the heart rate recovery at the second minute and third minute of recovery as the difference in heart rate at maximal exercise minus heart rate at the second minute and at the third minute of recovery. The first-degree slope of heart rate decline during the first minute of recovery (heart rate/t-slope) was also calculated.

The pulmonary rehabilitation program consisted of supervised aerobic exercise training, breathing control and relaxation techniques, methods of clearance of pulmonary secretions (performed by physical therapists), and psychological support on issues relating to chronic disability (administered by a psychiatrist). Subjects exercised on an electromagnetically braked ergometer (Ergociser EC1600, Cateye, Osaka, Japan) for 40 min/d. The sessions were conducted 3 times weekly for a total of 36 sessions (12 weeks). The exercise performed during the sessions was continuous. Subjects were instructed to exercise at an intensity that was initially equivalent to 60% of baseline maximum work load for 30 min each time. As training principles require the training intensity to parallel the improvement in physical fitness, the weekly training load was designed to represent 60% during weeks 1 to 3, 70% during weeks 4 to 6, and 80% of maximum work load during the last 4 weeks.

Statistical Analysis

Descriptive statistics for continuous variables are expressed as mean ± SD. The effect of rehabilitation on CPET and PFT parameters was assessed by paired *t* tests. To minimize bias secondary to violations of distributional assumptions in small sample sizes, we calculated confidence intervals (CIs) for the mean response of each parameter and *P* values with bootstrapping (1,000 replica-

Table 1. Pulmonary Function Test Parameters Before and After Rehabilitation

	Baseline	After Rehabilitation	Raw Difference	Bias-Corrected Difference	95% CI
FEV_1, % predicted	45.7 ± 18.7	47.5 ± 18.0	1.7	−1.4	−3.5 to 0.5
FVC, % predicted	78.3 ± 18.6	80.0 ± 17.0	1.7	−0.3	−5.2 to 4.6
FEV_1/FVC, %	44.6 ± 10.8	45.3 ± 13.5	0.7	−1.1	−2.6 to 0.4
PEF, % predicted	55.7 ± 20.3	58.4 ± 18.4	2.7	2.6	−1.1 to 6.6
FIVC, % predicted	75.4 ± 19.2	74.4 ± 20.8	−1.0	−1.4	−7.8 to 4.0
P_{Imax}, % predicted	65.3 ± 29.5	73.5 ± 28.0	8.2	8.1	−6.3 to 22.1

Values are mean ± SD. None of the differences are significant. Bias-corrected difference refers to the resampling (t) based estimate.
PEF = peak expiratory flow
FIVC = forced inspiratory vital capacity
P_{Imax} = maximal inspiratory pressure

tions with replacement, random-seed, CIs by percentile method).[28] To evaluate the effect size of the rehabilitation program on heart rate recovery parameters, we calculated the Cohen d statistic using the paired *t* test approach, as recommended by Rosenthal et al.[29] Of note, the pre- and post-rehabilitation values in our analysis had correlation of < 0.8, which is considered a threshold for effect overestimation.[30] To evaluate correlations between variables we used non-parametric statistical tests (Spearman correlation test). Significance was determined at the 2-sided $P = .05$ level. All analyses were performed with statistics software (Systat 12, Systat Software, San Jose, California).

Results

Baseline and post-rehabilitation values of PFTs parameters of the participants who completed the program are presented in Table 1. The exercise-based rehabilitation program had no significant effect on these parameters. Six subjects were withdrawn during the program: 4 subjects due to COPD exacerbation and 2 subjects due to nonadherence. Of the initial 45 subjects, 39 subjects (87%) completed the program (age 66.3 ± 7.8 y, 35 male, body mass index 27.1 ± 4.1 kg/m^2, FEV_1 45.7 ± 18.7%); all subsequent analyses refer to these subjects. All subjects reached a respiratory exchange ratio > 1. According to the updated GOLD classification, the subjects had severe COPD (stage III, FEV_1 30–50%). Subjects were receiving the following medications: inhaled β_2 agonists 100%, inhaled anticholinergic 100%, inhaled corticosteroid 100%, oral theophylline agents 95%, angiotensin converting enzyme/angiotensin-II receptor blocker 65%, chlorothiazide 35%, and statin 40%.

All subjects tolerated the exercise program well. During the 12-week course there were no cardiovascular or other events related to exercise requiring medical intervention or hospitalization. All subjects maintained an $S_{pO_2} \geq 90\%$ throughout exercise; however, 10 subjects needed oxygen supplementation during the exercise training.

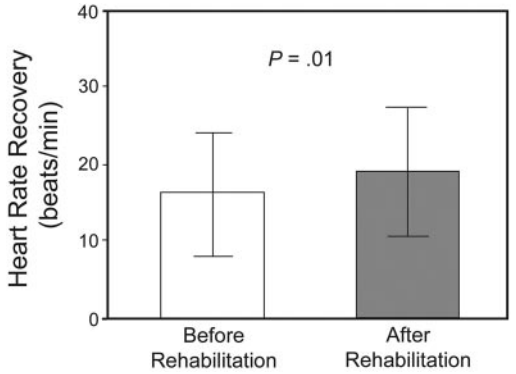

Fig. 1. Heart rate recovery before and after the rehabilitation program.

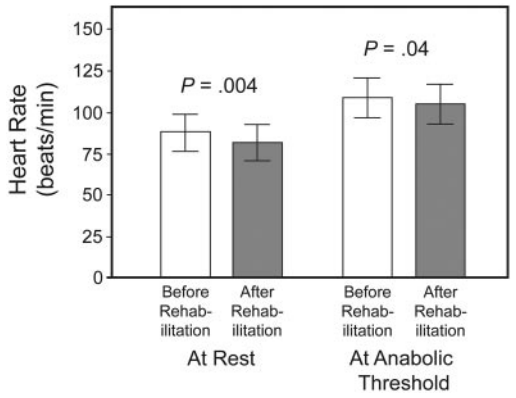

Fig. 2. Resting heart rate and heart rate at anaerobic threshold before and after the rehabilitation program.

After the rehabilitation program, heart rate recovery increased from 16.2 ± 8.0 beats/min to 18.4 ± 8.4 beats/min ($P = .01$) (Fig. 1), and heart rate at anaerobic threshold decreased from 109.0 ± 12.5 beats/min to 105.5 ± 11.7 beats/min ($P = .04$) (Fig. 2). In addition, resting heart rate decreased from 88.0 ± 10.7 beats/min to 83.3 ± 10.5 beats/min ($P = .004$), heart rate response from resting to anaerobic threshold increased from

Table 2. Parameters of Cardiopulmonary Exercise Testing Before and After the Rehabilitation Program

	Baseline	After Rehabilitation	Raw Difference	Bias-Corrected Difference	95% CI	*P*
Resting heart rate, beats/min	88.0 ± 10.7	83.3 ± 10.5	−4.7	−4.7	−7.7 to −1.7	.004
Heart rate at peak exercise, beats/min	131.6 ± 15.5	130.0 ± 17.7	−1.6	−2.0	−5.2 to 2.0	.42
Heart rate at first min recovery, beats/min	115.4 ± 13.4	111.6 ± 14.1	−3.8	−2.9	−7.6 to −0.1	.04
Heart rate recovery, beats/min	16.2 ± 8.0	18.4 ± 8.4	2.3	2.3	0.6 to 3.9	.01
$\dot{V}_{O_2}$ peak, mL/kg/min	14.3 ± 3.7	15.2 ± 3.8	0.8	0.8	0.2 to 1.5	.02
$\dot{V}_{O_2}$ at anaerobic threshold, mL/kg/min	9.7 ± 2.4	10.4 ± 2.6	0.7	0.7	0.1 to 1.3	.02
$\dot{V}_{CO_2}$ peak, mL/kg/min	1.09 ± 0.40	1.14 ± 0.44	0.05	0.05	−0.01 to 0.11	.10
$\dot{V}_E/\dot{V}_{CO_2}$	33.5 ± 8.1	31.9 ± 6.0	−1.6	−1.6	−3.2 to −0.2	.045
$\dot{V}_E/\dot{V}_{O_2}$	28.3 ± 10.2	27.1 ± 8.3	−1.2	−1.1	−3.1 to 0.7	.27
$\dot{V}_{O_2}$/t-slope, mL/kg/min^2	−0.32 ± 0.16	−0.38 ± 0.19	−0.06	−0.06	−0.10 to −0.02	.003
$t_{1/2}\dot{V}_{O_2}$ peak, s	123.0 ± 42.1	109.7 ± 42.1	−13.3	−13.2	−20.3 to −6.4	< .001
Work load max, W	65.8 ± 29.9	75.6 ± 34.2	9.8	9.9	5.6 to 14.4	< .001
Work load at anaerobic threshold, W	35.9 ± 18.6	45.2 ± 21.8	9.3	9.3	5.6 to 13.3	< .001
Duration, s	510 ± 202	568 ± 180	58	56	2 to 108	.042

Values are mean ± SD.
Bias-corrected difference = resampling (bootstrap) based estimate
$\dot{V}_{O_2}$ peak = maximal oxygen uptake
$\dot{V}_{CO_2}$ peak = maximal carbon dioxide output
$\dot{V}_E$ = minute ventilation
$\dot{V}_E/\dot{V}_{CO_2}$ = respiratory equivalent for CO_2
$\dot{V}_E/\dot{V}_{O_2}$ = respiratory equivalent for O_2
$t_{1/2}\dot{V}_{O_2}$ peak = time of carbon dioxide output ($\dot{V}_{O_2}$) decline to its half value during recovery
$\dot{V}_{O_2}$/t-slope = first-degree slope of $\dot{V}_{O_2}$ decline during the early recovery

17.4 ± 15.3 beats/min to 22.1 ± 13.3 beats/min ($P = .003$), and heart rate at the second minute and at the third minute of recovery decreased from 105.6 ± 11.9 beats/min to 103.3 ± 11.9 beats/min ($P = .045$), and from 101.3 ± 10.1 beats/min to 95.7 ± 11.9 beats/min ($P = .009$), respectively. Heart rate at maximal exercise was unchanged (131.6 ± 15.5 beats/min pre- vs 130.0 ± 17.7 beats/min post-rehabilitation, $P = .42$). There was no correlation between heart rate recovery and $\dot{V}_E/\dot{V}_{CO_2}$ slope before or after the program (data not shown). There was a significant correlation between heart rate recovery and resting heart rate before the rehabilitation program (rho = –0.48, $P = .003$), and between heart rate recovery and resting heart rate after the rehabilitation program (rho = –0.33, $P = .042$). However, the correlation between the difference of heart rate recovery before and after the program and the difference of resting heart rate before and after the program was marginal (rho = –0.31, $P = .055$). Heart rate/t-slope also increased from –16.0 ± 7.7 beats/min^2 to –18.0 ± 8.7 beats/min^2 after the program ($P = .008$). The effect size (Cohen d) for heart rate recovery was 0.42, which is considered a small to medium effect size.[31]

The parameters of CPET at baseline and after rehabilitation are shown in Table 2. $\dot{V}_{O_2}$-peak, $\dot{V}_{O_2}$ at anaerobic threshold, maximum work load capacity, work load at anaerobic threshold, and duration of exercise increased, while $\dot{V}_E/\dot{V}_{CO_2}$ decreased. $\dot{V}_{O_2}$/t-slope (Fig. 3) and $t_{1/2}\dot{V}_{O_2}$-peak (Fig. 4) were also improved.

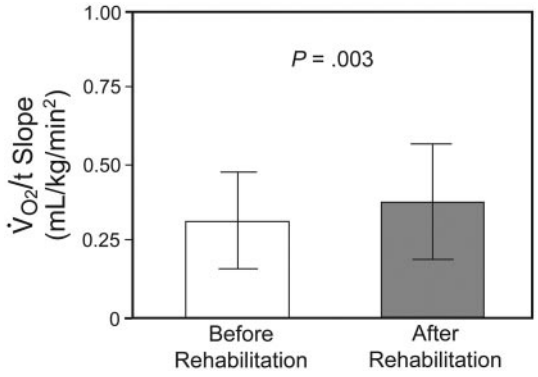

Fig. 3. Oxygen uptake ($\dot{V}_{O_2}$) over time slope before and after the rehabilitation program.

Parameters of ventilatory performance at baseline and after exercise training are shown in Tables 3 and 4, respectively. No change was observed in $\dot{V}_E$ at rest and at peak of exercise. However, a significant decrease was observed in $\dot{V}_E$ at the standardized work load (see Table 4). Similar trends were observed for respiratory rate, tidal volume, and $\dot{V}_E/\dot{V}_{CO_2}$, while inspiratory, expiratory, and total breathing cycle times at the standardized work load were significantly increased. Heart rate at the standardized work load was significantly decreased from 131.6 ± 15.5 beats/min to 126.6 ± 14.7 beats/min.

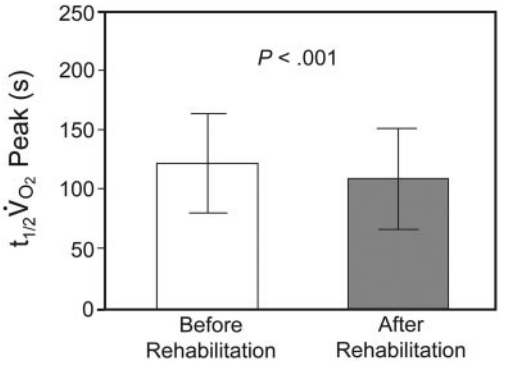

Fig. 4. Time for 50% decline of oxygen uptake ($t_{1/2}\dot{V}_{O_2}$) before and after the rehabilitation program.

Discussion

In our study, heart rate recovery increased and resting heart rate decreased following a supervised, exercised-based rehabilitation program in patients with COPD. These findings point to an exercise-mediated amelioration of the sympathovagal imbalance that characterizes COPD. Our findings are in line with previous work showing that exercise has beneficial effects on reconditioning of baroreflex sensitivity[32] and heart rate variability.[33,34]

The weight of evidence indicates that heart rate recovery is initially affected by parasympathetic reactivation, while later in the recovery it depends on both parasympathetic reactivation and sympathetic withdrawal.[35] On the other hand, resting heart rate reflects primarily the result of vagal tone and intrinsic heart rate, while the impact of sympathetic tone remains controversial.[36] Recent data suggest that sympathovagal imbalance leads to increased resting heart rate and impaired heart rate recovery in COPD patients.[5]

The level of vagal activation in COPD appears to be increased,[37] superimposed on an overactive sympathetic component.[38,39] This may be a result of certain drug effects as well as augmented sympathetic drive due to generalized neurohumoral activation and mechanical alterations of the chest cavity that characterize COPD.[38] The interaction between sympathetic and parasympathetic systems, which regulates autonomic control of the heart, has been traditionally viewed as opposite and reciprocal. However, evidence suggests that this interaction is both synchronous and synergistic.[40] This balance is pivotal for the effective and undisruptive function of all systems. This is true throughout exercise and recovery.[41] Thus, although parasympathetic activity is elevated in COPD,[37,42] its beneficial effect on heart rate regulation is blunted due to the overall imbalance of the autonomic system. Given that our subjects were on stable medical treatment throughout the study, we attributed the modest improvements in heart rate recovery and resting heart rate to a partial amelioration of autonomic dysfunction. Although the exact pathophysiologic mechanisms of this effect remain unclear, there are a number of potential explanations that merit further discussion.

First, previous studies have found striking similarities between COPD and heart failure regarding systemic effects and inflammatory-oxidative profiles,[38,43] and there are also reports linking autonomic dysfunction to these profiles.[44,45] Notably, exercise training improves the inflammatory-oxidative profile in heart failure,[46] COPD,[43] and other chronic diseases.[47] Second, exercise training has been shown to improve the skeletal muscle abnormalities of heart failure, with a resulting decrease in central sympathetic nerve outflow.[43,48] A similar modification has been observed in the muscles of COPD patients after exercise training,[43,49] suggesting another pathway that is favorably affected by exercise training. The observed increase in $\dot{V}_{O_2}$/t slope after program completion in our subjects implies skeletal muscle improvement. $\dot{V}_{O_2}$/t slope expresses the fast component of repayment of the O_2 debt; this period is called the alactic phase, because the excessive O_2 consumed is used to replete high-energy phosphate stores in skeletal muscle (rephosphorylation of creatine). The early rapid decline in oxygen consumption depends, at least partially, on the rate of this process. Improved skeletal muscles function could favorably affect autonomic function. In addition, the observed increase of $\dot{V}_{O_2}$ and work load at anaerobic threshold after exercise training indicates improvement in exercise performance of our subjects due to functional changes in the exercising muscles, allowing them to increase their capacity for aerobic work. This is also reinforced by the observed decrease in $\dot{V}_E/\dot{V}_{CO_2}$, suggesting an improvement in ventilatory efficiency. There is a strong link between ventilatory response, peripheral muscle,[50] and autonomic function.[51] Thus, the reduction in $\dot{V}_E/\dot{V}_{CO_2}$ points to an improvement of peripheral muscle function and lessening of the metabolic cost of breathing during exercise. We observed that rehabilitation reduced $\dot{V}_E$ and respiratory rate at standardized work load, pointing to substantial reductions in the ventilatory demand. The significant post-rehabilitation increase in expiratory time at standardized work load signifies improved lung emptying with each breath and more efficient breathing. The decrease in respiratory demand favorably alters the chest mechanics during exercise (reduces intrathoracic pressure) and ameliorates sympathetic overactivity.[52]

Plasma catecholamines have been shown to increase at work loads above the anaerobic threshold, and the increase in heart rate is steeper above this point, indicating a cardiovascular compensatory mechanism for the anaerobic stress.[53] The observed decrease of heart rate at anaerobic threshold after the completion of the program implies that exercise training has affected the way the autonomic nervous system regulates these cardiovascular adaptations. Furthermore, the increased slope or response of heart rate from resting to anaerobic threshold suggests an improvement of the balance

Table 3. Ventilatory Performance Parameters Before and After Rehabilitation

	Baseline	After Rehabilitation	Raw Difference	Bias-Corrected Difference	95% CI	*P*
Resting minute ventilation, L/min	13.8 ± 2.6	13.1 ± 3.2	−0.7	−0.6	−1.6 to 0.3	.17
Minute ventilation at peak of exercise, L/min	41.2 ± 12.0	42.7 ± 15.7	1.7	1.5	−2.0 to 4.5	.39
Resting respiratory rate, breaths/min	20.5 ± 6.2	19.2 ± 4.7	−1.3	−0.8	−1.9 to 0.3	.09
Respiratory rate at peak of exercise, breaths/min	32.7 ± 7.4	35.2 ± 7.4	3.3	2.4	1.0 to 3.9	.003
Resting tidal volume, L/min	0.72 ± 0.19	0.71 ± 0.21	−0.01	−0.02	−0.06 to 0.03	.52
Tidal volume at peak of exercise, L/min	1.28 ± 0.33	1.26 ± 0.34	−0.02	−0.01	−0.06 to 0.05	.78
Inspiratory time at peak of exercise, s	0.75 ± 0.20	0.72 ± 0.19	−0.03	−0.03	−0.06 to 0.01	.16
Expiratory time at peak of exercise, s	1.19 ± 0.35	1.13 ± 0.32	−0.06	−0.06	−0.11 to −0.01	.02
Total breathing cycle time at peak of exercise, s	1.93 ± 0.44	1.81 ± 0.45	−0.12	−0.08	−0.16 to −0.01	.043

Values are mean ± SD.
Bias-corrected difference = resampling (bootstrap) based estimate

Table 4. Parameters of the Ventilatory Performance at the Standardized Work Load

	Baseline	After Rehabilitation	Raw Difference	Bias-Corrected Difference	95% CI	*P*
Minute ventilation at standardized work load, L/min	41.2 ± 12.0	37.2 ± 12.4	−4.0	−4.0	−6.3 to −1.6	.003
Respiratory rate at standardized work load, breaths/min	32.7 ± 7.4	30.3 ± 7.3	−2.4	−2.0	−3.9 to 0	.040
Tidal volume at standardized work load, L/min	1.28 ± 0.33	1.21 ± 0.26	−0.07	−0.07	−0.14 to 0	.045
Inspiratory time at standardized work load, s	0.75 ± 0.20	0.81 ± 0.20	0.06	0.06	0.02 to 0.09	.009
Expiratory time at standardized work load, s	1.19 ± 0.35	1.27 ± 0.41	0.08	0.08	0.02 to 0.015	.02
Total breathing cycle time at standardized work load, s	1.93 ± 0.44	2.09 ± 0.53	0.16	0.17	0.07 to 0.27	.003
$\dot{V}_E/V_{CO_2}$ at standardized work load	40.1 ± 7.8	38.8 ± 6.8	−1.3	−1.3	−2.3 to −0.3	.002

Values are mean ± SD.
$\dot{V}_E$ = minute ventilation
$\dot{V}_E/V_{CO_2}$ = respiratory equivalent for CO_2

between sympathetic-parasympathetic nervous system, as their interaction is present throughout exercise.[41]

Our study has several limitations. First, we did not include a standard-care control group. However, beyond the improvement in heart rate recovery and resting heart rate, we observed concomitant improvement in multiple parameters, including $\dot{V}_E/\dot{V}_{CO_2}$, heart rate at anaerobic threshold, heart rate response from resting to anaerobic threshold, and ventilatory parameters at standardized work load. Thus, it is unlikely that the beneficial effects of exercise training are due to chance alone. In addition, although the subjects were allowed an initial run-in period to be familiarized with the laboratory, test, and procedures, we cannot exclude the possibility of a learning effect. Interestingly, in studies looking at the effects of rehabilitation on heart rate variability, standard-care subjects demonstrated no change in the time and frequency domains of heart rate variability, whereas a significant improvement was observed in subjects who participated in the rehabilitation program,[33] implying that the learning effect is limited. Second, we did not measure levels of inflammatory or oxidative markers in our subjects, as well as other possible factors affecting sympathovagal balance, which might be of relevance in this context. Thus, we were not able to establish a direct mechanistic link with our clinical findings. Finally, we excluded patients receiving heart rate-modulating medications (with the exception of COPD-specific medications). Thus, we could not control for the effect of these medications. Notably, use of β_2 agonists and anticholinergic agents in healthy young adults does not alter the autonomic control of cardiovascular system.[54] Also, like other systemic effects, tolerance has been demonstrated for the cardiovascular effects after long-term use of β_2 agonists.[55]

Notwithstanding these limitations, to our knowledge this is the first study showing an improvement of autonomic function in COPD patients after exercised-based rehabilitation, as substantiated by changes in resting heart rate and heart rate recovery after maximal CPET. Both resting heart rate and heart rate recovery have been shown to provide prognostic information in a large asymptomatic population,[56] and elevated resting heart rate has been associated with increased mortality in heart failure and ischemic heart disease.[57] Although the absolute effect of exercise rehabilitation on both resting heart rate and heart rate recovery in our study was relatively small, the effect size was small to medium. In addition, in prospective studies small dif-

ferences in baseline heart rate recovery have been associated with considerably different prognosis.[58] However, any effect on "hard" clinical outcomes would be difficult to demonstrate in a small population, highlighting the need for large, randomized outcome-driven studies. Rehabilitation programs are considered important therapeutic interventions that improve quality of life and make the everyday living of COPD patients easier. Whether this intervention exerts favorable effect on outcomes merits further investigation. Notably, rehabilitation has been shown to exert beneficial effects on heart rate related parameters in patients with heart failure also.[59,60] However, long-term training is needed to evoke a significant shift in baseline sympathovagal balance in heart failure.[61] This might well be the case with COPD also.

Conclusions

In conclusion, exercise training appears to improve the impaired balance of the autonomic nervous system in COPD patients. Can we consider rehabilitation as an additional therapeutic intervention in the effort to modulate sympathovagal imbalance in these patients? Given that this disturbance is present early in the course of the disease, the incidence of cardiac arrhythmias is high in COPD patients,[62,63] and physical activity is associated with an important reduction in the risk of all-cause and respiratory mortality in COPD patients,[64] early initiation of exercise-based rehabilitation programs might prevent some of the consequences of COPD and favorably affect mortality. Although, a number of important clinical questions remain unanswered, including the optimal initiation of exercise training, mode and intensity of exercise, and duration of training, an exercise-based rehabilitation program is an important therapeutic regimen for COPD patients. Organized and equipped facilities are needed, and physicians must encourage their patients to include exercise in their everyday activities.

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