CME Section

Exercise Training and Pulmonary Rehabilitation in the Pulmonary Hypertension Patient

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Recent evidence challenges the traditional wisdom regarding the risks of exercise in PAH patients. Clearly, there are some patients who benefit from the addition of pulmonary rehabilitation to their medical treatment. Still, the details regarding the optimal patient population, timing, and makeup of the program are undefined. As evidence mounts regarding the safety and benefits of an exercise regime in patients with PAH, pulmonary rehabilitation may become another tool to improve the quality of life for these patients.

Exercise training improves outcomes in patients with cardiopulmonary diseases such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD).[1,2] Because of this, formal rehabilitation programs are commonly used in management. Although the symptoms of pulmonary arterial hypertension (PAH) are similar to those in both CHF and COPD, data on the effects of exercise in PAH patients are minimal. Historically, exercise was discouraged for PAH patients due to concern that it would induce hypoxemia, arrhythmias, and worsening right ventricular failure.[3] However, results of recent studies have challenged this historical wisdom. Based on early data, the most recent American College of Chest Physicians (ACCP)/American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) evidence-based clinical practice guidelines suggest that pulmonary rehabilitation may be beneficial in PAH patients, although they offered no firm recommendation.[2] Experts in PAH continue to debate the safety versus potential benefit of an exercise program for these patients. The rationale for the ongoing investigation can be better understood by examining respiratory physiology in the patient with PAH.

EXERCISE PHYSIOLOGY IN PAH

One of the earliest symptoms of PAH is dyspnea with exertion. This symptom is related to complex alterations in normal exercise physiology. In response to physical exertion, muscle metabolism increases which then prompts an increase in respiratory rate and cardiac output to optimize oxygen delivery. The normal pulmonary circulation responds to this increased flow by recruiting vascular units and decreasing vascular resistance. These compensatory mechanisms are impaired in the patient with PAH. Cardiopulmonary exercise testing (CPET) allows observation of this physiologic change by measuring the ventilatory equivalent of carbon dioxide (VE/VCO_2), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and anaerobic threshold (AT). Using CPET, we are able to relate the pathophysiology of PAH to the patient's symptom of dyspnea with exertion.

Pulmonary arterial hypertension is characterized by abnormal remodeling of the adventitial, smooth muscle and intimal layers of the small pulmonary arteries. As disease burden increases, the pulmonary circulation transforms from a high flow/low resistance system to a low flow/high resistance system. This transformation affects exercise capacity in 2 ways. First, pulmonary arteries can no longer vasodilate to accommodate increased flow. Second, there are fewer "unused" and therefore available vascular units for recruitment. In normal controls, the ventilatory equivalent for carbon dioxide (VE/VCO_2) will decrease with exercise as respiratory rate increases and alveolar-capillary units are recruited. In PAH patients an increase in physiologic dead space, due to decreased perfusion in the remodeled pulmonary capillary bed and resultant ventilation/perfusion mismatch, alters this response. Thus VE/VCO_2 increases in PAH patients commensurate with the severity of disease.[4] Further, right to left intracardiac shunting with exercise in PAH patients with a patent foramen ovale will worsen this abnormal response to exercise.[4] Increased dead space ventilation in PAH patients is also confirmed by measuring the partial pressure of end-tidal CO_2 with exercise (Figure 1).[5] This mismatch between perfusion and ventilation of alveoli limits respiratory efficiency and likely contributes to dyspnea.

The cardiac output response to exercise is also altered in PAH. Cardiac magnetic resonance imaging (MRI) studies reveal an impaired stroke volume response in PAH patients when compared to normal controls.[6] This impairment in stroke volume results from both an increase in pulmonary artery pressure (PAP) with exercise and a decrease in left ventricular volume as the enlarged right ventricle geometrically impairs diastolic filling. This low output state decreases oxygen delivery to the exercising muscle, resulting in lactic acidosis and a further increase in ventilatory drive. Thus, this pathological response to exercise creates a spiral of increasing respiratory drive and decreasing cardiopulmonary efficiency.

In addition to limitations in cardiac output and pulmonary vascular capacitance, PAH patients also have altered peripheral oxygen extraction. Tolle et al recently compared exercise hemodynamic and CPET parameters in patients with PAH, diastolic heart failure, and systolic heart failure (Figure 2).[7] This comparison revealed a significant decrease in oxygen extraction at maximal exercise in patients with mild PAH when compared to patients with left sided heart failure. The cause of this difference is unclear, but perhaps the ongoing vasculopathy in pulmonary hypertension induces a more

Key Words—cardiac output, cardiopulmonary exercise testing, dyspnea, idiopathic pulmonary arterial hypertension, 6-minute walk distance
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"systemic" inflammation, with distant effects on muscle metabolism. Mainguy et al evaluated exercise capacity, quadriceps strength, enzymatic profiles, and muscle biopsy pathology in 10 patients with idiopathic PAH (IPAH).[8] Pulmonary arterial hypertension patients had a lower proportion of type I muscle fibers, a higher potential for anaerobic metabolism, and lower quadriceps strength than matched controls. These results suggest that skeletal muscle dysfunction may also contribute to dyspnea in patients with PAH.

EXERCISE TRAINING

The observation that exercise limitation in PAH affects quality of life prompts the question of whether this might be amenable to intervention. To this end, recent work has examined whether an exercise training program might be safe and effective in PAH patients. Mereles et al, working in Germany, published the largest work on this subject in 2006.[9] This multicenter study group recruited 30 patients into a 15-week randomized controlled exercise and lifestyle modification protocol. Patients were either classified as having PAH (n=23) or chronic thromboembolic pulmonary hypertension (n=7), were World Health Organization (WHO) functional class II-IV, and had been on a stable medical regimen for at least 3 months.

Patients were randomized into a training group or a sedentary group. Patients in each group were monitored in the hospital for the initial 3 weeks of the protocol. The primary end points of the study were 6-minute walk test (6MWT) distance and health related quality of life as measured by the Short Form Health Survey (SF-36). Secondary end points included Borg dyspnea index, changes in WHO functional class, stress echocardiographic parameters including estimated PAP and right ventricular and atrial areas, and CPET parameters. These end points were evaluated at baseline, Week 3, and Week 15.

The program was intensive and both the control and the intervention groups received a nutritional program, physical therapy, massages, counseling, respiratory training, and muscular relaxation while in the hospital. The intervention

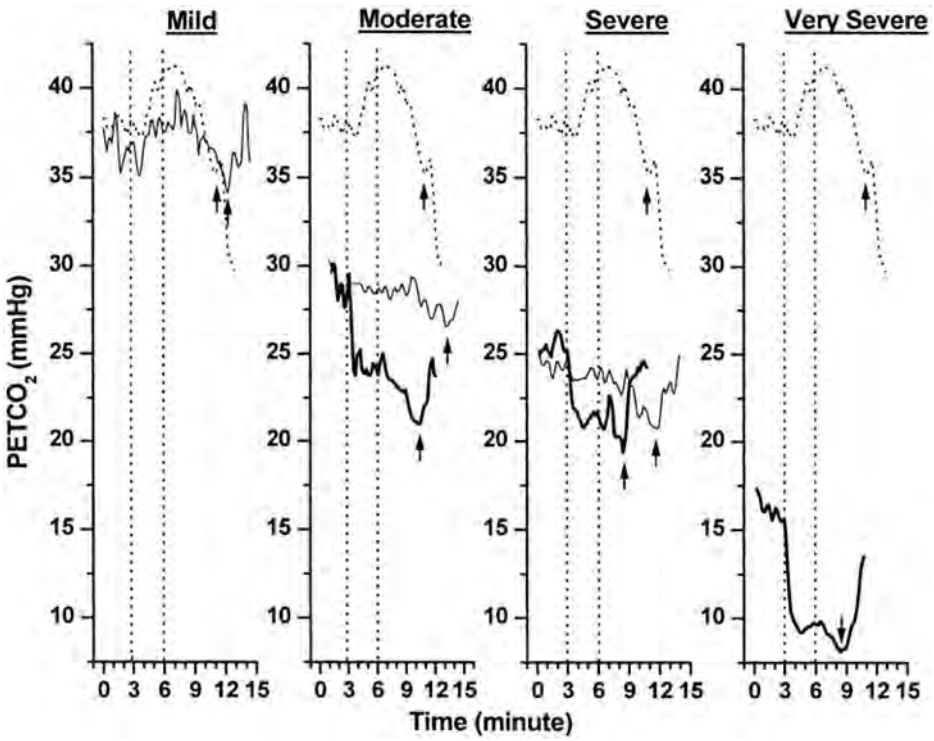

Figure 1: $PETCO_2$ vs time curves for patients with PAH and exercise induced right to left intracardiac shunt (bold line), PAH and no intracardiac shunt (thin continuous line), and a normal control (dotted line). The arrows indicate the end of the exercise period. The dotted line at 3 minutes is the beginning of unloaded pedaling. The dotted line at 6 minutes indicates increasing work rate exercise. Patients are grouped by the severity of their pulmonary hypertension. Reprinted with permission of American College of Chest Physicians: Yasunobu Y, et al. *Chest*. 2005;127(5):1637-1646.

group additionally underwent a supervised, 7-day-a-week regimen of 10 to 25 minutes of interval-graded bicycle ergometer training which was limited by peak heart rate <120, SpO_2 <85% and perceived physical exertion. Additionally, they performed 60 minutes of walking on level and uphill ground 5 days per week during which they were accompanied by a physiotherapist and received "mental

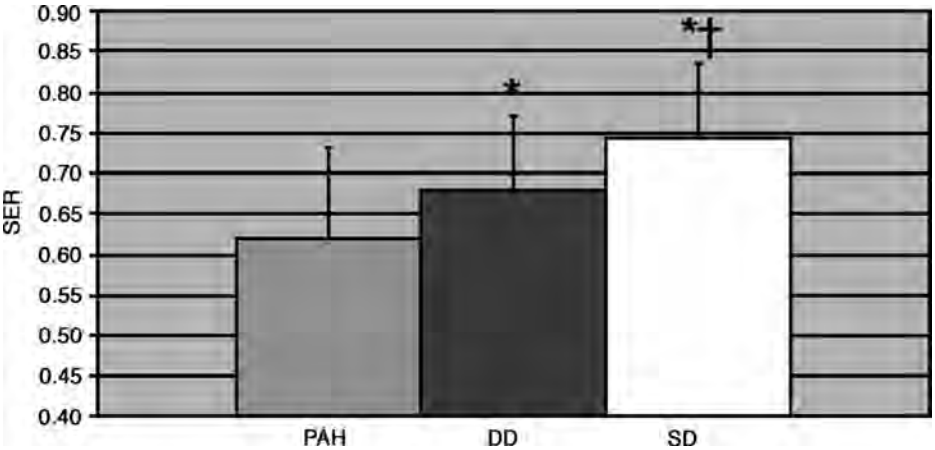

Figure 2: Systemic O_2 extraction at maximum exercise. SER, systemic extraction ratio; PAH, pulmonary arterial hypertension; DD, diastolic dysfunction; SD, systolic dysfunction. **P*<0.05 vs PAH; †*P*<0.05 vs DD. Reprinted with permission from Tolle J, et al. Impaired systemic oxygen extraction at maximum exercise in pulmonary hypertension. *Med Sci Sports Exerc*. 2008;40(1):3-8.

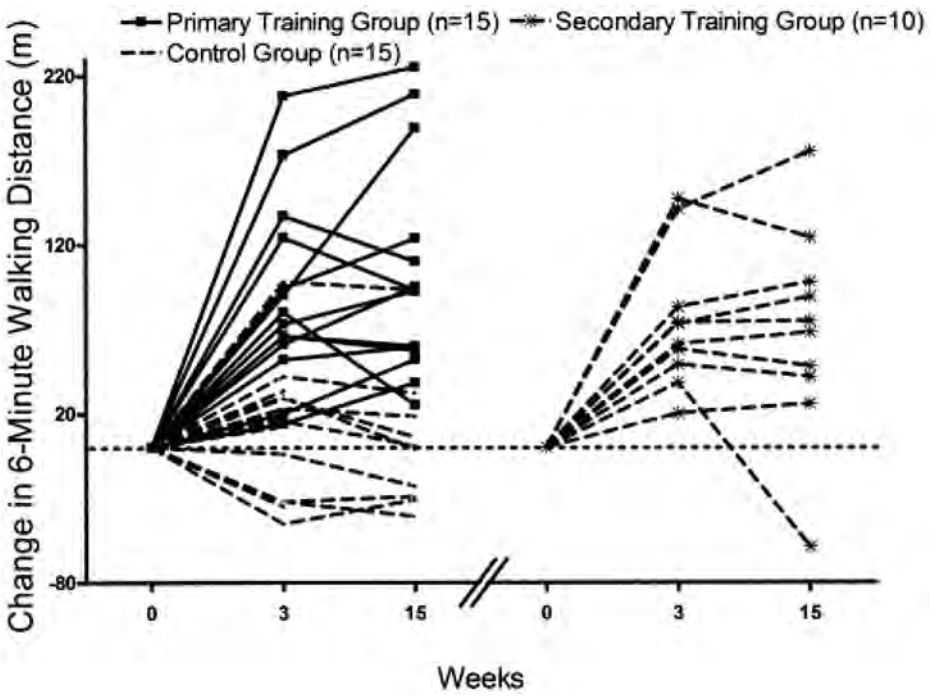

Figure 3: Mean (SE) change in 6-minute walking distance from baseline to Week 15 in the primary training, control, and secondary training groups.**P*=0.0003 for primary training vs control group after 3 weeks of training; *****P*<0.0001 for primary training vs control group after 15 weeks of training; ***P*<0.05 for secondary training group vs control group after 3 weeks of training; ***P*=0.001 for secondary training group vs control group after 15 weeks of training. Reprinted with permission from Mereles D, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. ***Circulation*. 2006; 114(14):1482-1489.**

training" to improve their perception of their physical abilities. Five days per week they performed 30 minutes of dumbbell training and 30 minutes of respiratory training. They also participated in yoga and "strengthening of respiratory muscles." After the 3-week in-hospital program, they were discharged with an individualized training manual and a bicycle ergometer. They were instructed to use the bicycle for a total of 15-30 minutes, 5 times per week, at their target heart rate. They also were instructed to continue their respiratory exercise and dumbbell training every other day. They were monitored by phone during the at-home period. After the initial 15-week period, the sedentary group was offered the same training regimen and 10/15 participated, comprising a secondary training group.

All patients had severe PAH with mean pulmonary vascular resistance of 902±358 dynes·cm^{-5} in the sedentary group and 969±44[4] dynes·cm^{-5} in the training group. Baseline WHO functional class was primarily III (73%), with the remainder of patients classified as II (20%) and IV (7%).

The results of this intensive training regimen were significant. At baseline the groups had similar 6MWT distances at 411±86 m in the control group and 439±82 m in the training group (P=0.38). After completion of the 15-week program the mean difference in the 6MWT distance between the groups was 111 m (P<0.001) (Figure 3). The secondary training group also showed 6MWT improvement at 3 weeks and after completion of the program. Quality of life scores were lower in patients at baseline compared with the general population. The physical training program improved the physical and mental component summation scores on the SF-36 and the subscale scores for physical functioning, mental health, and vitality. WHO functional class improved significantly in the training group as did peak oxygen consumption (VO_2 peak 11.4±3.3 ml·min^{-1}·kg^{-1} vs 15.4±3.7 ml·min^{-1}·kg^{-1}). The ventilatory equivalent of carbon dioxide at anaerobic threshold decreased in the primary training group after 3 weeks but increased in sedentary patients. There were no adverse events during the program such as right heart failure or progression of symptoms or disease.

This was the first prospective, randomized, controlled trial to show that a regimented exercise training program can positively impact quality of life and exercise parameters in patients with PAH. Despite these exciting results, the findings in this study must be interpreted with caution. Improvement in 6MWT distance as a result of training does not indicate improvement in pulmonary hemodynamics, as it might in response to pharmacologic therapy for PAH. In addition, the population studied in the Mereles paper excluded patients with connective tissue diseases.

CARDIOPULMONARY REHABILITATION

In 2009, a group in Amsterdam examined the effect of a 12-week outpatient program on 6MWT distance and CPET parameters. This study also examined the effect of strength training by assessing quadriceps function with a hydraulic dynamometer and muscle biopsy at baseline and after training.[10] Additionally, endurance was measured using submaximal exercise with both aerobic and resistance training. All patients in this program were diagnosed and treated for IPAH. They attended a training program at a rehabilitation center 3 times per week, which utilized the American Heart Association guidelines for the rehabilitation of chronic heart failure patients.[11] Briefly, this program consisted of cycling and resistance training targeted at the quadriceps. At the end of the trial period, there were no changes in 6MWT distance or peak exercise capacity. However. their exercise endurance time increased and their anaerobic threshold shifted toward a higher workload (32±5 to 46±6 W, P=0.001). Quadriceps strength increased by 13% (P=0.005), but there was a larger change

in muscle endurance at 34% ($P=0.001$). Quadriceps muscle biopsy showed increased capillary formation and oxidative enzyme activity after training. This study showed that an outpatient, intermittent program can improve endurance and muscle aerobic capacity.

A similar but smaller study was recently reported from Quebec.[12] In this trial, 5 IPAH patients treated with a single oral agent were recruited into a 12-week outpatient cardiopulmonary rehabilitation program. Baseline 6MWT, CPET, endurance cycle testing, and volitional and nonvolitional quadriceps strength at maximal voluntary contraction (MVC) were measured. These measurements were then used to create an exercise prescription for each patient. Patients attended the program 3 times per week, which consisted of: 10-15 minutes of cycling with workload personalized to CPET, resistance exercises consisting of 2 sets of 10-12 repetitions for 6-8 different muscle groups, and 15 minutes of treadmill walking at 85% of mean 6MWT speed. The intensity of the program was then increased as tolerated. The following parameters were measured before and after the program: 6MWT, cycle endurance test, limb muscle cross-sectional area, quadriceps function by maximal voluntary contraction and magnetic stimulation, and muscle biopsy. At the end of the training period, patients exhibited a mean increase of 13% in 6MWT distance and a 53% increase in endurance time. Additionally VE/VCO_2 decreased after training. The proportion of type IIx muscle fibers decreased, while type I muscle fiber increased and the capillary/fiber ratio increased. The authors postulate that this "less fatigable" muscle profile might contribute to a higher anaerobic threshold after training. This study also suggests that in patients with IPAH, exercise endurance can be improved by exercise training.

The magnitude of the improvement noted in these trials rivals medical therapy. In fact, the STRIDE-1 study group utilized CPET data when evaluating the safety and efficacy of sitaxsentan in PAH.[13] Although the primary end point (peak VO_2) was reached for the highest dose of the drug, none of the other CPET parameter changes were statistically significant. Medical therapy is targeted toward the pathology of pulmonary arteriopathy, and should be optimized and stable before increasing cardiopulmonary demand with an exercise program. The addition of exercise training targets cardiovascular fitness and muscle strength, thereby improving oxygen delivery, oxygen uptake, and ultimately endurance.

FUTURE DIRECTIONS

These studies reveal that a careful and regimented exercise program may improve endurance and symptoms in PAH patients. Still, many questions remain unanswered regarding the optimization of these programs. These studies included patients who had been on a stable PAH treatment regimen for a number of months. The optimal timing for initiation of a program remains unknown. Additionally, reported programs had varying ratios of strength versus aerobic exercise. Although it is likely that a combination of both strength and endurance training is helpful, the optimal combination is also unknown. Further work is needed to determine if results from studies such as that reported in the Mereles paper can be reproduced completely in the outpatient setting and in broader patient populations. Ongoing work in the area of exercise pathophysiology and programs in patients with PAH will help answer some of these remaining questions.

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