Exercise Training in Pulmonary Hypertension
Implications for the Evaluation of Drug Trials

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The response to exercise training reported in this issue of Circulation1 should change the way we perceive and treat selected patients with pulmonary hypertension (PH) and brings into focus the problem of measuring the effects of drug therapy in this condition.2

In a highly structured 15-week program of daily exercise, patients with PH experienced a mean increase of 96±61 meters in the 6-minute walking test from a baseline of 439±82. The increase in the 6-minute walking distance after exercise training was greater than that achieved with prostacyclin formulations, endothelin receptor antagonists,3 and phosphodiesterase inhibitors. By comparison, the baseline and incremental increases in the 6-minute walking distance in studies of successful drug therapies range from a low of 297±31 meters with epoprostenol4 to 342±51 with sildenafil.5 The study group consisted of 24 patients with idiopathic pulmonary arterial hypertension and 6 patients with chronic thromboembolic PH. Fifteen patients were initially entered into the active exercise program, and 15 control patients crossed over to the exercise program after the first 15 weeks. Although not explicitly stated, it appears that there were no patients with the scleroderma spectrum of disease entered in the study, presumably because of the inability to exercise. Other patients with musculoskeletal limitations were excluded as well. Clearly, the cohort in the present study had a higher baseline physical capacity than patients reported in most drug trials, and this may be partly responsible for the greater increase in 6-minute walk than previously reported.

The exercise program was both comprehensive and intense. Patients were hospitalized for the first 3 weeks and exercised under supervision 7 days a week. The exercise program had 3 components: Patients rode a cycle ergometer to 60% to 80% of maximal heart rate for 10 to 25 minutes, walked for 60 minutes 5 days per week on flat and uphill grades, and performed 30 minutes of low-weight dumbbell lifting 5 days a week. All patients had a physiotherapist in attendance and underwent fitness education. For the remainder of the study, patients were asked to cycle 15 to 30 minutes 5 days per week and to continue respiratory and dumbbell training, with regular telephone follow-ups. A small additional increase in 6-minute walk of 11 meters suggests that patients adhered to the outpatient program.

The study by Mereles et al1 shows that exercise capacity and quality of life can be enhanced in patients with PH using a training program. Not only did the 6-minute walk improve, but workload at the anaerobic threshold increased and VO₂max increased from 13.2 mL·min⁻¹·kg⁻¹ to 15.4 mL·min⁻¹·kg⁻¹. Most patients were in World Health Organization class III (mean 2.8) at outset, and there was a trend toward reduction to class II (mean 2.4) at the end of the study. Baseline hemodynamic variables did not change substantially over the course of the program except for a small reduction in systolic pulmonary arterial pressure. The increase in VO₂max was small, and much of the improvement in dyspnea may have been related to the increase in workload at the anaerobic threshold from 45 to 65 W. On the basis of these results, published recommendations for the general management of PH will need reconsideration.6,7

Should we be surprised that exercise training is safe and useful in severe PH? Based on reported experiences in advanced left heart failure where exercise training improves function and quality of life,8,8 this study was overdue. We now know that carefully designed exercise is safe and useful in the short term in PH. The benefits are likely to be similar to those found with exercise in left heart failure, including improvement in strength and endurance in non-cardiac muscles, as well as reduced anxiety and increased confidence during physical activity. The study by Mereles et al1 was not designed to test whether exercise training improves survival, so no conclusions can be made with regard to long-term effects. Most of the changes in measured variables during the exercise program were favorable to reduction in right heart work (pulmonary artery systolic blood pressure, maximum heart rate, increased anaerobic threshold), but resting heart rate was not reduced. In left heart failure, exercise training has well-documented beneficial effects on cardiopulmonary function.10,11 Despite inferences drawn from small cohorts, no exercise study has clearly demonstrated prolonged survival in congestive heart failure. Thus, although exercise training is an adjunctive therapy that can improve quality of life of patients with PH, it cannot yet be equated with therapies that improve survival.

A dilemma in the design of clinical trials in PH is the length of study needed to document a survival benefit. The majority of studies in PH measure efficacy as the change in the 6-minute walk over a period of only 12 to 16 weeks of treatment. It will be very difficult to design studies to test
whether an exercise program gives a durable improvement in cardiopulmonary function over longer periods of time or improves survival. It also might be difficult and dangerous to enroll patients in an exercise regimen before the initiation of drug therapy. However, the response to exercise training highlights a degree of uncertainty that exists in the PH community about how to assign clinical value to variations in the 6-minute walk. This study\(^1\) raises the questions of what level of fitness or training should be expected or documented before a baseline 6-minute walk in patients entered into drug trials and whether concomitant exercise training should accompany drug therapy.

Although the results of the study by Mereles et al\(^1\) are impressive, they cannot be assumed to represent the responses of a larger cohort of patients with PH. Although the group of 30 patients was randomly entered into either the initial or subsequent exercise group, little is said about original recruitment criteria. Presumably, these were highly motivated and otherwise fit individuals willing and able to suspend their normal lives during an experiment of high intensity that obligated patients to remain in the hospital for 3 weeks. This kind of exercise training would be virtually impossible to implement broadly in populations that included primary family wage earners, those with insufficient health-care coverage, and those living a great distance from the treatment center or with no access to local rehabilitation facilities. A caveat to this study is that it was a program of high intensity in a selected subset of patients. The feasibility of its implementation in a large population of patients with PH is problematic, and therefore its general applicability to all patients with PH is unproven.

In summary, this is an important study\(^1\) that shows that exercise training can have an impact on short-term functioning and well-being in selected patients with PH that is equal to the best current drug therapies. Whether this effect is durable or improves survival is unknown. The study does suggest that fitness training should be considered for all patients with PH at some point in their treatment plan, recognizing that not all patients will be capable or will qualify. Because exercise training has short-term effects on exercise performance that are similar to drug therapies, future studies will need to account for fitness and conditioning.

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Disclosures

None.

References


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