Editorial
Exercise training as a form of cardiovascular therapy in chronic heart failure

Romualdo Belardinelli, Ernesto Faccenda, Loretta Volpe, Stefania Balestra, Giampiero Perna

Department of Cardiology, Hospital "G.M. Lancisi", Ancona, Italy

(Ital Heart J 2000; 1 (10): 653-655)

Received August 11, 2000; accepted August 17, 2000.

Address:

Dr. Romualdo Belardinelli

Dipartimento di Cardiologia
Azienda Ospedaliera "G.M. Lancisi"
Via Rismondo, 5
60100 Ancona
E-mail:
r.belardinelli@fastnet.it

In the last decade, the demonstration that exercise may improve functional capacity and quality of life of patients with chronic heart failure has opened an interesting debate among cardiologists about the modality of exercise programs, the effects of exercise on the heart, and its clinical implications[1-4]. Although these preliminary results are encouraging, many questions are not yet answered and need to be clarified.

We will briefly discuss the selection of patients and the methodology of exercise training, the effects of exercise on coronary vessel and myocardial perfusion, and finally we will introduce recent results on the outcome.

Patient selection

The *conditio sine qua non* to obtain benefits from exercise training is patients' clinical stability. In all studies, patients enrolled did not have severe ventricular arrhythmias, unstable angina, and signs or symptoms indicating deterioration of heart failure in the last 3 months. Over this time, they were not hospitalized for worsening heart failure, nor they needed to modify the type or dosage of medications. Moreover, the majority of patients were in sinus rhythm, but atrial fibrillation did not represent a contraindication to exercise training.

Age. In a recent review, the mean age of patients studied was 59 ± 14 years[5]. The average increase in peak oxygen consumption (VO_2) after training was above 10% from the initial value in all decades. However, above 70%, the improvement in functional capacity was lower.

Sex. There are no differences in the results of physical training between women and men with identical age and clinical picture. The proportion of women is quite lower (1:4).

Medications. The combination of standard medications for heart failure with exercise does not influence the response to training programs. Patients involved in exercise training receive more frequently ACE-inhibitors, nitrates and diuretics, and less frequently cardioselective beta-blockers and antiarrhythmics.

Functional class. More than 60% of patients are in NYHA functional class II, and 30% are in class III. Pre-training peak VO_2 is between 15 and 17 ml/kg/min and is not correlated neither with left ventricular ejection fraction, nor with the response to exercise training. This is an important issue that should be taken into consideration when patients are referred to physical training. Patients with an ejection fraction < 30% can have a normal functional capacity, and they can improve their peak VO_2 more than 10% or 2-4 ml/kg/min from the initial value.

Left ventricular diastolic filling. An interesting finding is that the pattern of left ventricular diastolic filling can predict not only the response to exercise training, but also the outcome of patients with chronic heart failure[6]. Patients with an abnormal relaxation pattern (low early filling, high late fill-

ing, prolonged deceleration time) generally have a greater increase in peak VO_2 after training, and also a better prognosis. By contrast, patients with a restrictive pattern of left ventricular filling do not improve functional capacity after training, and also have a worse prognosis at 3 years. A greater early diastolic filling is associated with a higher stroke volume as well as peak VO_2, because of a lower left ventricular end-diastolic pressure and a lower transmitral gradient.

Etiology. As recently shown, almost two thirds of patients had ischemic heart disease, 20% idiopathic dilated cardiomyopathy and 10% valvular heart disease. Extensive coronary artery disease with left ventricular dysfunction and chronic heart failure are now considered as two new clinical indications to exercise training, because potential risks of exercising are overwhelmed by demonstration of benefits[1-5].

Methodology of exercise training

The results of exercise training programs are conditioned not only by patient selection, but also by the choice of the program. There is agreement in preferring aerobic exercise to isometric or eccentric exercise. The combination of an initial warm-up of calisthenics or stretching exercise with cycling on a stationary cycle ergometer is more effective in improving functional capacity than cycling alone[5]. Electrocardiographic monitoring by telemetry is indicated in patients with arrhythmias or stable angina, and it is used in all patients during the initial 2 weeks of training. Blood pressure and heart rate are measured at rest before each session, at peak exercise and during recovery. After a warm-up phase (10-15 min), patients exercise on a stationary cycle ergometer or a treadmill or both for 30 min. Before and after the work phase, a short (3-5 min) loadless exercise is recommended. The intensity of the work phase is selected on the basis of a symptom-limited exercise test. Since peak VO_2 is a more accurate indicator of work tolerance than heart rate, it is preferable to measure gas exchange during exercise and prescribe the intensity of the exercise regimen on the heart rate corresponding to 50-70% of peak VO_2. There is evidence that major benefits are obtained with programs of aerobic exercise at 60% of peak VO_2, 3 times a week for a minimum of 8 weeks. Long-term programs are more effective than short because benefits are maintained for a longer time[7]. The results of a recent randomized controlled trial have shown that two exercise sessions per week for 1 year can determine a sustained improvement in peak VO_2. Supervision by a cardiologist is preferable, especially in patients with severe chronic heart failure and with psychological problems. However, unsupervised home-based programs, more popular in northern Europe, are also effective[5]. The occurrence of untoward cardiac events is very low (< 3%). The most common are premature contractions and post-training hypotension. Studies are concordant in reporting high compliance to training. Supervised programs, however, have a higher compliance than home-based programs (85-90 vs 75-85%).

Coronary artery adaptations

Although an improvement in functional capacity after exercise training is mainly related to peripheral adaptations[8,9], recent studies have demonstrated myocardial and coronary vessel changes that can contribute to clinical benefits[7,10-12]. In patients with ischemic cardiomyopathy, a common finding is the coexistence of epicardial coronary artery stenoses with different amounts of necrotic, ischemic, hibernating and normal myocardial cells. There is evidence that 1) the presence of significant coronary stenoses in one or more epicardial vessels does not prevent an increased functional capacity with training programs; 2) the identification of hibernating dysfunctional myocardium is associated with a sensitivity of 70% and a specificity of 77% for predicting an increase in peak VO_2 after training[13]; and 3) exercise training can attenuate unfavorable remodeling in postinfarction patients with left ventricular dysfunction[14]. After short-term moderate exercise training an improvement in left ventricular contractility is correlated with increases in coronary collateralization as well as thallium uptake[10]. Since no changes in the morphology and severity of epicardial stenoses have been demonstrated, the improved myocardial perfusion seems mainly explained by functional and/or structural adaptations of small coronary vessels. A possible explanation may be an increased endothelium-dependent relaxation of coronary arteries induced by chronic exercise[11]. This effect has also been described in peripheral arteries after short-term programs[15]. Another explanation may be an angiogenetic effect of exercise. In the presence of a significant stenosis, intermittent bouts of exercise stimulate the expression of vascular endothelial growth factor and nitric oxide genes through a hypoxia-related mechanism[16,17]. New microvessels are generated, that in part organize into large collaterals, and in part potentiate myocardial microcirculation. Adenosine concentration in the interstitium of the myocardium is also increased after chronic exercise and can contribute to coronary collateral and vessel growth[18,19].

An unifying hypothesis may be that exercise training improves regional myocardial perfusion through an indirect effect of opening pre-existing collaterals and a direct effect of neoformation of small vessels. The former is due to functional adaptations of major coronary arteries determining a pressure difference between stenotic and normal arteries; the latter is related to two mechanisms: one is dependent on adenosine, another may be related to growth factors. An improvement in capillary diffusion capacity has been demonstrated in animals, and should be confirmed in humans[20]. At present, no direct demon-

stration exists that an improvement in flow-mediated dilation of conduit arteries can improve myocardial perfusion. This is an intriguing hypothesis that needs to be demonstrated. Moreover, the clinical significance of these adaptations requires larger studies.

Outcome

A recent trial has demonstrated, for the first time, that a long-term program of supervised exercise training improved the survival of patients with chronic heart failure[7]. Trained patients, after 1214 ± 56 days of follow-up, had a 63% reduction in cardiac mortality and a 71% lower rate of hospital readmission for heart failure than untrained controls. Cost-effective analysis pointed out that patients' life can be prolonged on average by additional 2.16 years at the low cost-effectiveness ratio of $1494 per life-year saved (personal data). An independent predictor of survival was post-training thallium uptake, suggesting that the improvement in myocardial perfusion after exercise training is more important than the severity and the number of coronary artery stenoses.

Conclusions

There is mounting evidence that exercise is a form of cardiovascular therapy which potentiates the effects of standard pharmacological interventions and determines important biological and clinical benefits in patients with chronic heart disease. Nowadays, interest is focusing on the prognostic significance of the clinical benefits of exercise training and on the mechanisms of these improvements. Exercise, if correctly designed and performed, can be considered an adjunctive therapeutic tool in the management of chronic heart failure as well as ischemic heart disease. Larger studies are needed in order to confirm these benefits in other cardiac disorders and to assess the prognostic significance in a larger population.

References

1. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation and autonomic function. Circulation 1992; 85: 2119-31.
2. Jettè M, Heller R, Landry F, Blumchen G. Randomized 4-week exercise program in patients with impaired left ventricular function. Circulation 1991; 84: 1561-7.
3. Coats AJ, Adamopoulos S, Meyer P, et al. Effects of physical training in chronic heart failure. Lancet 1990; 335: 63-6.
4. Kavanagh T, Myers GH, Baigrie RS, et al. Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months' aerobic training. Heart 1996; 76: 42-9.
5. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure: protocol and patient factors in effectiveness in the improvement in exercise tolerance. Eur Heart J 1998; 19: 466-75.
6. Belardinelli R, Georgiou D, Cianci G, et al. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy. Clinical and prognostic implications. Circulation 1995; 91: 2775-84.
7. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure. Effects on functional capacity, quality of life, and clinical outcome. Circulation 1999; 99: 1173-82.
8. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation 1988; 78: 506-15.
9. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995; 25: 1239-49.
10. Belardinelli R, Georgiou D, Ginzton L, et al. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 1998; 97: 553-61.
11. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 2000; 342: 454-60.
12. Laughlin MH, McAllister RM. Exercise training-induced coronary vascular adaptation. J Appl Physiol 1992; 73: 2209-25.
13. Belardinelli R, Georgiou D, Purcaro A. Low dose dobutamine echocardiography predicts improvement in functional capacity after exercise training in patients with ischemic cardiomyopathy: prognostic implication. J Am Coll Cardiol 1998; 31: 1027-34.
14. Giannuzzi P, Temporelli PL, Corrà U, et al. Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial. Circulation 1997; 96: 1790-7.
15. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation 1996; 93: 210-4.
16. Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. Circ Res 1994; 74: 349-53.
17. White FC, Roth DM, Baigrie RS, et al. Exercise induced coronary collateral development: a comparison to other models of myocardial angiogenesis. In: Schaper W, Schaper J, eds. Collateral circulation. Norwell, MA: Kluwer Academic Publishers, 1993: 261-89.
18. Ethier MF, Chander V, Dobson JG Jr. Adenosine stimulates proliferation of human endothelial cells in culture. Am J Physiol 1993; 265: H131-H138.
19. Meininger CJ, Granger HJ. Mechanisms leading to adenosine-stimulated proliferation of microvascular endothelial cells. Am J Physiol 1990; 258: H198-H206.
20. Laughlin HN, Tomanek RJ. Myocardial capillarity and maximal capillary diffusion capacity in exercise trained dogs. J Appl Physiol 1987; 63: 1481-6.