Review

Exercise and Cardiovascular Diseases

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Key Words

Exercise • Cardiovascular diseases • Cardiac rehabilitation • Prevention

Abstract

Exercise is a physiologic stressor that has multiple beneficial effects on cardiovascular system. Currently exercise training is a class I intervention as part of a multifactorial long-term process that includes: clinical assistance, assessment of global cardiovascular risk, identification of specific objective for each cardiovascular risk factor, formulation of an individual treatment plan with multiple intervention aimed at reduction of the risk, educational programs, planning of long term follow-up. This paper reviews the evidences of benefit of exercise in the most common heart diseases and describes the role of exercise training in the cardiac rehabilitation programs.

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Introduction

The relationship between exercise and cardiovascular diseases changed, evolving from proscription to prescription. In the 1930s the survivors of acute coronary syndromes were advised to rest in bed at least 6 weeks. Nowadays exercise training (ET) is considered class I intervention as a part of a rehabilitation program [1]. Similarly, in the 1980s restriction of physical activity was considered the cornerstone of the treatment of heart failure. Currently ET is a class I intervention in stable patients with heart failure [2]. A number of factors led to this radical change in medical opinion, including progress in knowledge of biology of exercise, of modalities of prescription of exercise and of safety issues, not to mention the demonstration of the effects of multifactorial cardiac rehabilitation services in the prevention of cardiovascular diseases [3].

Now ET is a fundamental part of cardiac rehabilitation (CR), a branch of cardiology defined as "the sum of activities required to influence favorably the underlying cause of the disease, as well as to ensure the patient the best possible physical, mental and social

conditions, so that they may, by their own efforts, preserve or resume when lost, as normal a place as possible in the life of the community" [4]. The aim of this paper is to review the evidences of benefit of exercise and the role of ET in the cardiac rehabilitation (CR) programs.

Effects of Exercise on Cardiovascular System

Prolonged ET induces functional and structural adaptations of cardiovascular, respiratory, musculoskeletal and metabolic systems. The quality and the size of the changes depend on the type, intensity and duration of the physical activity performed. Exercise can be classified according to the tension and the length of the working muscles. Isometric (or dynamic exercise) is the result of the contraction of large muscle group that leads to movement, as in running. Dynamic exercise increases heart rate and stroke volume with an increase of cardiac output as end result. The increase of heart rate is proportional to the intensity of exercise in young and middle-aged subjects, while in the elderly patients the chronotropic response is often exaggerated. Systolic blood pressure tends to increase linearly to the workload, while diastolic blood pressure is stable or lowers. At the same time, a redistribution of cardiac output occurs toward the working muscles (changing from nearly 20% at rest up to 85% at the acme of the effort) to the heart and to the brain occurs during exercise. Isometric exercise (e.g. the static hand grip) is the consequence of the contraction of smaller muscle group without movement. This type of exercise produces an increase of the vascular resistance and blood pressure, small effects on cardiac output and oxygen uptake. Free-weight lifting is the prime example of the third type of exercise, resistive exercise, in which a combination of movement and muscular contraction occurs. In the field of cardiac rehabilitation, dynamic exercise is the most helpful one for the prevention of cardiovascular diseases, while the static and resistive exercises are useful when the patients are already conditioned, in order to improve endurance [5]. Structural changes, as concentric left ventricular hypertrophy, alterations in myocytes (increase in number of mitochondria and myofibrils, increase in lactic dehydrogenase and pyruvate kynase activity), alterations in coronary arteries (increase in cross sectional area) and in coronary microcirculation (coronary collateral formation) have been described in the animal model as a result of prolonged training program. Recent advances in stem cell research and molecular biology shed light on the mechanism of the benefits of exercise in the domain of endothelial function, endothelial repair, arterial stiffness, micro RNA and collateral growth (recently reviewed by Schuler G et al.) [6].

Complex molecular changes induced by ET lead to activation of eNOS and therefore to vasodilatation and increased perfusion via the higher concentration of vascular nitric oxide. Moreover, the mechanism proposed for the mobilization of endothelial progenitor cells and mesenchymal stem cells caused by exercise is the activation of bone marrow stromal-cell-derived eNOs in the presence of matrix metalloproteinase-9. After mobilization, ET up regulates the cell receptor CCR-4, fundamental for the tissue engraftment of the mobilized cells. ET reduces arterial stiffness possibly contrasting the accumulation of advanced glycation end products that lead to the cross linking of collagen. Furthermore ET increase the arteriogenesis in the myocardium through the recruitment of progenitor cells and the production of growth factor as VEGF. A novel and promising field of research is represented by micro RNAs, small non-coding RNA molecules which regulate the gene expression. By means of acting on the expression of specific micro RNAs, ET may interfere with activation of eNOS (miRNA-21), angiogenesis (miR-126) and collagen synthesis (miR-29).

Role of Exercise in Cardiac Rehabilitation Programs

In the early days of CR, nearly 60 years ago, ET was the main intervention offered in CR programs, aimed at helping the patients in the recovery phase after myocardial

infarction. Nowadays ET is a part of a multifactorial long-term process that includes: clinical assistance, assessment of global cardiovascular risk, identification of specific objective for each cardiovascular risk factor, formulation of an individual treatment plan with multiple intervention aimed at reduction of the risk, educational programs, planning of long term follow-up [7].

Core Components of Cardiac Rehabilitation Programs

- Patient assessment
- Physical activity counselling
- Exercise training
- Nutritional counselling
- Weight control management program
- Lipid management
- Blood pressure management
- Smoking cessation
- Psychosocial management

Considerable knowledge was acquired on safety and modality of prescription of exercise. If the patient is carefully screened before the beginning of the program and supervised during the sessions, the CR can be considered safe. In a survey of CR programs the rates of non-fatal myocardial infarction and cardiac mortality were 1 per 294,000 patient-hours and 1 per 784,000 patient hours respectively [8].

As regards of exercise, task of the physician is to prescribe an exercise program tailored to the needs, comorbidity and to the functional capacity of the single patient. The prescription of exercise is somewhat similar to the prescription of drugs, including the definition of intensity, frequency, duration, type and rate of progression. This process is individualized and considers functional capacity and comorbidity. For example in patients with chronic kidney disease, which are a frequently admitted to cardiac rehabilitation program because cardiovascular disease is the principal cause of morbidity and mortality in this population, the planning of the cardiac rehabilitation program needs to consider that they more often have lower physical capacity due to multiple factors (anemia, myopathy, polyneuropathy, physical inactivity, immunosuppressive therapy). The ET will include resistance and endurance exercise, a specific exercise program for the lower body and an appropriate dietetic counseling [9]. Furthermore, the physician must counsel the patient about how to be more physically active during the leisure time.

Benefits of Exercise-Based Cardiac Rehabilitation Programs

Cardiovascular risk factors

ET can have a favorable effect on cardiovascular system acting on several cardiovascular risk factors. A meta-analysis of 72 trials on the effects of dynamic exercise showed that training induced significant net reductions in resting and daytime ambulatory blood pressure of, respectively, 3.0/2.4 mmHg ($P < 0.001$) and 3.3/3.5 mmHg ($P < 0.01$) with a more evident reduction in resting blood pressure hypertensive patients ($-6.9/-4.9$) than in the others ($-1.9/-1.6$; $P < 0.001$ for all) [10]. ET can reduce triglyceride levels (-5.6%), but is ineffective against total and LDL cholesterol concentration [11]. The effect of ET on HDL cholesterol is modest and it is modulated by genetic factors [12]. As regards of smoke, only 1 out of 15 trials documented an effect of ET on smoking cessation [13], therefore it has only a complementary role in tobacco cessation programs.

Chronic ischemic heart disease

Taylor et al. analyzed nearly 9000 patients recruited in 48 trials published before 2003 [14]. Compared with usual care, cardiac rehabilitation was associated with reduced all-cause mortality (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.68 to 0.93) and cardiac mortality (OR = 0.74; 95% CI: 0.61 to 0.96); better control of total cholesterol level, triglyceride level, and systolic blood pressure and smoking. There were no significant differences in the rates of nonfatal myocardial infarction and revascularization, and in changes of diastolic blood pressure, HDL and LDL cholesterol levels.

The cardiac rehabilitation maintains its efficacy also in the current therapeutic context. More recently Heran et al. conducted a systematic review of 47 studies randomizing more than 10,000 patients to exercise-based cardiac rehabilitation or usual care. In medium to longer term (i.e. 12 or more months follow-up) cardiac rehabilitation reduced overall and cardiovascular mortality [RR 0.87 (95% CI 0.75, 0.99) and 0.74 (95% CI 0.63, 0.87), respectively], and hospital admissions [RR 0.69 (95% CI 0.51, 0.93)] in the shorter term (< 12 months follow-up), but did not reduce the risk of total MI, CABG or PTCA. In a sub-group analysis, in seven out of 10 trials there was a significantly higher level of quality of life in participants to cardiac rehabilitation programs [15].

After percutaneous coronary intervention

Patients with coronary artery disease who received percutaneous coronary intervention (PCI) may benefit from ET. In ETICA trial, 118 patients who underwent PCI were randomized to six-month period of ET or usual care. At the end of program, trained patients showed significant improvement in functional capacity and quality of life. At the end of follow up the restenosis rate was similar in the two groups. The trained patients showed a lower rate of combined endpoint of mortality, myocardial infarction percutaneous coronary intervention or coronary artery bypass graft (log-rank 8.15, $p = 0.005$) and of hospitalization than control group [16].

In a community based study, the impact of cardiac rehabilitation on mortality and cardiac events after PCI was assessed retrospectively in 719 patients who underwent cardiac rehabilitation programs and a matched pair control group. The cardiac rehabilitation participants showed 46% relative reduction in all-cause mortality in CR (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.41 to 0.71; $p < 0.001$). The benefit was similar irrespectively of age, sex and setting of PCI (elective versus non-elective procedures) [17].

After coronary artery bypass graft

The benefit of attending cardiac rehabilitation after CABG is highlighted by a recently published community based study in which 529 patients included in CR were compared with 264 patients who did not [18]. CR attendance was associated with a significant reduction in 10-year all-cause mortality after CABG: the relative risk reduction in all-cause mortality was 46% (hazard ratio, 0.54; 95% confidence interval, 0.40–0.74; $P < 0.001$) and the 10-year absolute risk reduction was 12.7% (number needed to treat=8). The effect was similar independently of age, sex, diabetes and previous myocardial infarction.

Heart failure

Patients with heart failure were admitted to exercise-based cardiac rehabilitation more recently. Multiple trials have shown that exercise programs are safe and that exercise capacity can be improved [19, 20]. As regards of mortality, the results are conflicting. A meta-analysis conducted in 800 patients enrolled in 9 studies showed that ET significantly reduced mortality (HR 0.65, CI 0.46-0.92 $p = 0.015$) and the combined endpoint of mortality or hospitalization (HR 0.72, CI 0.56-0.93 $p = 0.011$) [20]. Disappointingly, the results of a randomized clinical trial published in 2009 [21] did not confirm the effect on mortality. The meta-analysis of The Cochrane Collaboration confirmed the lack of effect on total mortality [22]. A possible explanation may come from a single-centre study published in 2012 [23]. One hundred twenty-three stable chronic heart failure patients were randomized to an intense

ET supervised program conducted in a coronary club or to usual care. At the end of the 10-year study, the trained patients had a better work capacity, a better quality-of-life score and significant lower rate of hospital readmission and cardiac mortality (hazard ratio 0.68, $p < 0.001$). Albeit the study was designed to assess the effect of ET on functional capacity, it suggests that a program that significantly improves the functional capacity, conducted for a prolonged period of time, can have an impact on hard endpoints.

Peripheral artery disease

Peripheral artery disease is a common comorbidity of patients attending CR programs. A meta-analysis published in 1995 demonstrated that exercise training to near-maximal pain for at least six months was beneficial in improving walking distance [24]. More recently, a Cochrane analysis of exercise rehabilitation programs for claudication compared training with non-exercised control groups. Twenty-two trials involving a total of 1200 participants with stable leg pain were analyzed. Compared with usual care or placebo, exercise significantly improved maximal walking time: mean difference 5.12 minutes (95% confidence interval (CI) 4.51 to 5.72;) walking distances were also significantly improved: pain-free walking distance mean difference 82.19 meters (95% CI 71.73 to 92.65) and maximum walking distance mean difference 113.20 meters. (95% CI 94.96 to 131.43). Improvements were seen for up to two years [25].

Conclusion

Exercise is a physiologic stressor that can have multiple beneficial effects on cardiovascular system. A better understanding of the molecular mechanisms of the benefits are foreseeable in a near future, but evidences collected so far are adequate to consider exercise a fundamental tool in the prevention of cardiovascular diseases if adequately prescribed and supervised. Other tools – drugs, patient education, behavioral and psychological management – must be employed in a multidisciplinary, coordinated, long-term approach in order to promote the cardiac prevention and to ameliorate the quality of life of patients affected by heart disease. Therefore in the continuum of care offered to the patient affected by cardiovascular disease, cardiac rehabilitation, is at the end of acute care and at the beginning of long-term, life-long, care. Nevertheless, CR is underutilized: only one third of coronary artery disease patients receive any form of CR [9]. Evidences of benefits of exercise and CR are worth spreading among cardiac care intensivists, interventional cardiologists, cardiac surgeons and health care managers and policy makers in order to break down barriers to the participation of cardiac patients to CR programs.

Disclosure Statement

The authors state that they do not have any conflicts and nothing to disclose.

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References

- 1 The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg G, James SK, Atar D, Badano LP, Blömostrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, Widimsky P, van 't Hof A, Zahger D: ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-2619.
- 2 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787-1847.
- 3 Wenger NK, Froelicher ES, Smith LK, Ades PA, Berra K, Blumenthal JA, Certo CM, Dattilo AM, Davis D, DeBusk RF, et al.: Cardiac rehabilitation as secondary prevention. Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute. *Clin Prat Guidel Quick Ref Guide Clin* 1985;17:1-23.
- 4 Rehabilitation after cardiovascular diseases, with special emphasis on developing countries: report of a WHO Committee. *World Health Organ Tech Rep Ser* 1993;831:1-122.
- 5 Fletcher GF, Flipse TR, Oken KR: Exercise and the cardiovascular system; in Fuster V, Alexander W, O'Rourke RA (eds): *Hurst's the heart*. 11th ed. New York McGraw-Hill, 2004.
- 6 Schuler G, Adams V, Goto Y: Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives. *Eur Heart J* 2013;34:1790-1799.
- 7 Giannuzzi P, Saner H, Björnstad H, Fioretti P, Mendes M, Cohen-Solal A, Dugmore L, Hambrecht R, Hellemans I, McGee H, Perk J, Vanhees L, Veress G; Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology: Secondary prevention through cardiac rehabilitation. *Eur Heart J* 2003;24:1273-1278.
- 8 Van Camp SP, Peterson RA: Cardiovascular complications of outpatients cardiac rehabilitation programs. *JAMA* 1986;256:1160-1163.
- 9 Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP; Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation: Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;17: 1-17.
- 10 Pattyn N, Cornelissen VA, Toghi Eshghi SR, Vanhees L: The Effect of Exercise on the Cardiovascular Risk Factors Constituting the Metabolic Syndrome. A Meta-Analysis of Controlled Trials. *Clin Nutr* 2012;31:156-167.
- 11 Kelley GA, Kelley KS: Comparison of aerobic exercise, diet or both on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Clin Nutr* 2012;31:156-167.
- 12 Blazek A, Rutsky J, Osei K, Maisyeu A, Rajagopalan S: Exercise- mediated changes in high-density lipoprotein: impact on form and function *Am Heart J* 2013;166:392-400.
- 13 Ussher MH, Taylor A, Faulkner G: Exercise interventions for smoking cessation. *Cochrane Database Syst Rev* 2012;1:CD002295.
- 14 Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skudmore B, Stone JA, Thompson DR, Oldridge N: Exercise-based rehabilitation for patients with coronary heart disease: systematic review and metaanalysis of randomized controlled trials. *Am J Med* 2004;116:682-692.
- 15 Heran BS, Chen JMH, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS: Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011;7:CD001800.
- 16 Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A: Exercise training after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol* 2001;37:1891-1900.

- 17 Goel K, Lennon RJ, Tilbury TR, Squires RW, Thomas RJ: Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation* 2011;123:2344-2352.
- 18 Pack QR, Goel K, Lahr BD, Greason KL, Squires RW, Lopez-Jimenez F, Zhang Z, Thomas RJ: Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery. A community-based study. *Circulation* 2013;128:590-597.
- 19 Rees K, Taylor RS, Singh S, Coats AJS, Ebrahim S: Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;3:CD003331.
- 20 Piepoli MF, Davos C, Francis DP, Coats AJ: Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;328:189-196.
- 21 O'Connor C, Whellan DJ, Lee KL, Keteleyan SJ, Cooper CS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Houston Miller N, Flegg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL: Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439-1450.
- 22 Davies EJ, Moxham T, Rees K, Singh S, Coats AJS, Ebrahim S, Lough E, Taylor RS: Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2010;4:CD003331.
- 23 Belardinelli R, Georgiou D, Cianci G, Purcaro A: 10-Year exercise training in chronic heart failure. A Randomized controlled trial. *J Am Coll Cardiol* 2012;60:1521-1528.
- 24 Gardner AW, Poehlman ET: Exercise rehabilitation programs for the treatment of claudication pain. A meta analysis. *JAMA* 1995;274:975-980.
- 25 Watson L, Ellis B, Leng GC: Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2008;4:CD000990.