Physical activity in the reduction of cardiovascular risk - too good to be prescribed?

Jose Kawazoe Lazzoli

Biomedical Institute, Fluminense Federal University, Niterói - RJ, Brazil; Cardiology Division, Cor Diagnose / Santa Teresa Hospital, Petrópolis - RJ, Brazil; Member of the Executive Committee (Treasurer), International Federation of Sports Medicine (FIMS).

Introduction

A major goal in Cardiovascular Medicine is to prolong life expectancy, while maintaining quality of life. We may consider that, in order to maintain a healthy and physiologically competent cell renewal process, an important factor would be health of the cardiovascular system. The efferent vessels play a pivotal role in the capacity of our organic structure to preserve long-lasting normal function, by supplying necessary substances to every living cell in our body. Thus, vascular health would be equal to longer life.

Many characteristics are potentially deleterious to vascular health, such as the well-known risk factors hypertension, diabetes, dyslipidemia, and smoking. In the clinical setting, such agents are hugely injurious to endothelial health, leading to long-term development of atherosclerotic disease, that would - by this reasoning - abbreviate length of a disease-free life, and reduce life expectancy.

In fact, most of the diseases that may shorten life expectancy are cardiovascular and interrelated, such as coronary artery disease, heart failure, cerebrovascular disease, chronic heart failure, and peripheral artery disease. These disorders share a common factor - atherosclerotic disease, the end result of vascular aggression.

Most of the clinical studies that support different therapeutic interventions (like statins, betablockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker agents, antiplatelet agents) to reduce cardiovascular risk aim to prevent or to postpone both these diseases and cardiovascular acute events like acute myocardial infarction or stroke. Physical activity (PA) or physical exercise (PE), when performed regularly, produce a series of physiological adaptations which contribute to reduced cardiovascular risk. But can they produce effects similar to those drugs, with an impact on hard endpoints such as acute cardiac events or mortality?

Physical activity in the reduction of cardiovascular risk

Physical activity (PA) has been long recognized as an important instrument to reduce all-cause and cardiovascular mortality. Since several reports in ancient India, China, and Greece, until the classical transversal study in London bus and postal workers[1], there seemed to be a positive relationship between PA and health. Although the mechanisms remained unclear for many years, a number of prospective studies in the last decades of the 20th Century have shown the association between an active lifestyle and the reduction of mortality[2-4].

Most of those studies have shown that a given weekly energy expenditure was associated with a reduced all-cause and/or cardiovascular mortality, while others have shown that the inclusion of moderate to high-intensity activities would lead to further reduction of mortality[5]. In fact, functional capacity (FC) was found to predict cardiovascular risk in apparently healthy individuals or subjects with cardiovascular diseases, with mean reductions around 13-15% for each additional metabolic equivalent (MET) of FC[6,7]. Thus, physical fitness and PA are clearly associated with reduced mortality rates[8-11].

According to these data, it is important to fulfill some predominantly aerobic PE characteristics: volume (duration of each session times frequency), and intensity (assessed as a percentage of maximal oxygen uptake or maximal heart rate), to obtain training effects that will ultimately enhance FC. Strengthening exercises may also produce positive health effects. This leads to a concept of a given mode of exercise, with a dosage, to be individually prescribed, to enhance the beneficial effects, with minimal or no risk. Accordingly, we would be working within a therapeutic range: if the dosage would be too low, the benefits would not appear as expected; and if the dosage would be too high, we would enter into a "toxic dosage", with eventual side-effects, like injuries or risk of sudden death, depending on the subject's clinical characteristics. PE must, therefore, be individually and properly prescribed, the same way we would do with statins, anti-hypertensive agents, betablockers or antiplatelet agents.

Mechanisms

Obviously, controlling the classical risk factors for cardiovascular diseases would reduce cardiovascular risk. Thus, better control of the blood pressure levels in hypertensive subjects; better glycemic control in the diabetic patients; a better cholesterol control in dyslipidemic individuals; reducing fatty mass in obese patients: all these interventions

Correspondencia: Jose Kawazoe Lazzoli
E-mail: jkl@uninet.com.br

could produce health benefits and all these clinical conditions may be improved by adopting an active lifestyle, or by performing regularly prescribed PE.

The effects of PA on lipids are also long well-recognized. Regular PE produces an important reduction in triglycerides, mild reductions in total cholesterol and LDL-cholesterol (with an important modification on its composition, with bigger, less dense, and less atherogenic particles), and an increase in HDL-cholesterol levels. This is mainly mediated by a lipoprotein lipase increased activity, and a decreased hepatic triglyceride lipase activity.

Changes in body composition, influenced by PA or PE, with a reduction of fatty mass, preferably with the preservation of lean body mass, are associated with better blood pressure, glycemia, and lipids control.

The association between regular PE and reduced sympathetic tone, with preserved cardiac vagal tone has long been recognized[12]. This has been demonstrated to enhance cardiac electrical stability, which protects against sudden cardiac death, and is associated with a better prognosis in coronary artery disease and heart failure patients. Proper electrocardiographic criteria for vagotonia have been described[13].

Regular PA has also been associated with improved endothelial function, both in coronary patients and healthy subjects[14]. Endothelial dysfunction leads to a diminished capacity for regulating blood flow to skeletal muscles and myocardium during high-intensity exercise, that would lead to a hypertensive response to exercise and/or myocardial ischemia. The enhancement of endothelial function is one of the mechanisms of blood pressure control in hypertensive subjects.

Also, physical conditioning can alter fibrinolytic variables and fibrinogen, with an increase in tissue-type plasminogen activator (t-PA) activity, an increase in the percentage of t-PA in the active form, a decrease in plasminogen activator inhibitor type 1 (PAI-1) activity, and a decrease in fibrinogen. These group of variables would theoretically lead to a reduction in the probability of acute vascular events, like an acute myocardial infarction or a stroke[15]. High-sensitivity C-reactive protein is an inflammatory marker also related to atherosclerotic disease, that may be significantly reduced by exercise training[16].

In the field of the surrogate markers, with clinical relevance still to be proved, we can include the positive association between PA and endothelial progenitor cells[17,18]; we can remember that central vascular stiffness tends to be decreased in active subjects, mainly mediated by decreased plasma endothelin-1 levels, and by increased plasma nitric oxide levels[19]; and that a reduced carotid wall thickness progression has been associated with high-intensity exercise habits[20].

Physical exercise in the cardiovascular and metabolic diseases

Most subjects with cardiovascular and metabolic diseases are high-risk patients and, according to current clinical consensus, must follow very rigorous goals for LDL-cholesterol levels. Most of these patients will be, at least, on antiplatelet agents and statins. What we observe in clinical practice is when a cardiac patient performs regular PE, it becomes easier to keep them tightly within the LDL-cholesterol goals, probably with a lower statin dosage. Experimental data suggest also a stabilization effect of long-term PE on the atherosclerotic plaques[21], that is a major expected effect of antiplatelet agents and statins on atherosclerotic disease.

The role of exercise-based cardiac rehabilitation programs has been long recognized in reducing mortality and cardiac events in post-infarction patients[22,23]. Regular PE in coronary artery disease (CAD) patients has been shown to improve myocardial perfusion and to retard disease progression. PE also produces a positive influence on inflammatory and fibrinolytic variables[15,16], and on endothelial function[14], which augments the stability of CAD. In selected stable CAD patients, PE has been shown to be an interesting alternative to coronary angioplasty[24,25], and if it is performed, PE reduces the incidence of acute events[26]. But the main effect is probably the increase in functional capacity, that has been shown to be a strong predictor of mortality and myocardial infarction in CAD patients[27]. It does not mean, obviously, that we must chose only one treatment modality; if properly indicated, the patient may benefit from interventionist treatment (either angioplasty or coronary bypass surgery), or pharmacological treatment and PE as well[28].

Exercise training is an important adjunct non-pharmacological treatment modality for patients with heart failure (HF), that has proved to provide positive effects on mortality, morbidity, exercise capacity and quality of life. PE improves not only central parameters, but also reverses the so-called skeletal muscle failure[29], commonly observed as the main cause of physical impairment in these patients. Classical studies have shown the enhancement of autonomic balance[30], the correction of endothelial dysfunction[31] and FC-dependent reduction on mortality[32-34]. Also, it has been demonstrated that not only peripheral factors are involved, but also central factors contribute to a better clinical outcome[35,36]. In fact, PE has been incorporated as class IA recommendation in recent guidelines for HF patients to improve functional capacity and symptoms[37].

It has been observed that blood pressure (BP) levels in hypertensive subjects tend to be lower (most of studies show an acute reduction of 6 to 15mmHg) after each mild-to-moderate intensity aerobic exercise session[38]. The maintenance of these lower levels would last approximately 24 hours[39], what would be an example of a "sub-acute" effect, in which the "chronic" effect would be no more than the summation of the "acute" effects. For a hypertensive subject, we can think of PE like a medicine to be taken once a day to assure a good BP control, the same way an anti-hypertensive agent (like an angiotensin-receptor blocker) would act and would be taken. Besides predominantly aerobic exercises, muscular strength exercises were also demonstrated to produce health benefits in hypertensive patients[40].

PA is today a well-recognized intervention in diabetic patients. The central mechanism is an optimized peripheral insulin utilization, with an enhanced insulin sensitivity. This produces lower insulin and glycemic levels. The mechanisms include both non-insuline mediated and insulin-mediated glucose disposal. Similarly to insulin, a single bout of exercise increases the rate of glucose uptake into the skeletal muscles, the process being regulated by the translocation of GLUT4 glucose transporters to the plasma membrane and transverse tubules. Also, physical exercise increases insulin-stimulated glucose uptake. Endurance exercise further increases lipid oxidation, and glycogen reserve utilization, with the effect of an increased insulin sensitivity, which would last from 48

to 72 hours after each exercise session (what we could also consider as a "sub-acute" effect)[41].

Conclusion

In conclusion, physical activity and/or physical exercise, when performed regularly, are valuable tools to reduce cardiovascular risk, by a series of mechanisms, leading to a better control of the classic cardiovascular risk factors that are injurious to vascular health, and reducing all-cause and cardiovascular mortality. Functional capacity is a strong predictor of cardiovascular risk, with an important impact on the reduction of mortality. Some of these effects can be produced by the use of pharmacological interventions, but the increase of functional capacity can be obtained by physical training only. Isn't it time to review our prescription to our patients, including also physical exercise as a powerful tool to help reduce cardiovascular risk and to prolong life?

References

1. Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JW. Coronary heart disease and physical activity of work. *Lancet.* 1953;265:1053-7.
2. Paffenbarger Jr RS, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med.* 1986;314:605-13.
3. Paffenbarger Jr RS, Hyde RT, Wing AL, Lee I-M, Jung DL, Kampert JB. The association of changes in physical activity level and other lifestyle characteristics with mortality among men. *N Engl J Med.* 1993;328:538-45.
4. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc.* 2009;41:998-1005.
5. Paffenbarger Jr RS, Lee I-M. Physical activity for health and longevity. *Res Q Exerc Sport.* 1996; 67(suppl 3):11-28.
6. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood E. Exercise capacity and mortality among men referred for exercise testing. *N Eng J Med.* 2002;346:793-801.
7. Kokkinos P, Myers J, Kokkinos JP, Pitaras A, Narayan P, Manolis A, *et al.* Exercise capacity and mortality in black and white men. *Circulation.* 2008;117:614-22.
8. Blair SN, Kohl HW 3rd, Barlow CE, Paffenbarger Jr RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. *JAMA.* 1995;273:1093-8.
9. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, *et al.* Gait speed and survival in older adults. *JAMA.* 2011;305:50-8.
10. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality. *J Am Coll Cardiol.* 2014;64:472-81.
11. Holme I, Anderssen SA. Increases in physical activity is as important as smoking cessation for reduction in total mortality in elderly men: 12 years of follow-up of the Oslo II study. *Br J Sports Med.* 2015;49:743-8.
12. Billman GE. Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention. *J Appl Physiol.* 2002;92:446-54.
13. Lazzoli JK, Soares PP, da Nobrega AC, de Araujo CG. Electrocardiographic criteria for vagotonia-validation with pharmacological parasympathetic blockade in healthy subjects. *Int J Cardiol.* 2003;87:231-6.
14. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, *et al.* Effect of exercise on endothelial function in patients with coronary artery disease. *New Eng J Med.* 2000;342: 454-60.
15. Stratton JR, Chandler WL, Schwartz RS, Cerqueira MD, Levy WC, Kahn SE, *et al.* Effects of physical conditioning on fibrinolytic variables and fibrinogen in young and old healthy adults. *Circulation.* 1991;83:1692-7.
16. Milani RV, Lavie CJ, Mehra MR. Reduction in C-Reactive Protein through cardiac rehabilitation and exercise training. *J Am Coll Cardiol.* 2004;43:1056-61.
17. Laufs U, Werner N, Link A, Endres M, Wassmann S, Jürgens K, *et al.* Physical training increases entothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation.* 2004;109:220-6.
18. Walther C, Gaede L, Adams V, Gelbrich G, Leichtle A, Erbs S, *et al.* Effect of increased exercise in school children on phyisical fitness and endothelial progenitor cells – a prospective randomized trial. *Circulation.* 2009;120:2251-9.
19. Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, *et al.* Effect of habitual exercise on body weight and arterial function in overweight and obese men. *Am J Cardiol.* 2009;104:823-8.
20. Kozàkovà M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Balkau B. Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population. *Eur Heart J.* 2010;31:1511-9.
21. Pellegrin M, Miguet-Alfonsi C, Bouzourene K, Aubert JF, Deckert V, Berthelot A, *et al.* Long-term exercise stabilizes atherosclerotic plaque in ApoE knockout mice. *Med Sci Sports Exerc.* 2009;41:2128-35.
22. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. *JAMA.* 1988;260:945-50.
23. O'Connor GT, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger Jr RS. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation.* 1989;80:234-44.
24. Hambrecht R, Walther C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, *et al.* Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease - a randomized trial. *Circulation.* 2004;109:1371-8.
25. Walther C, Möbius-Winkler S, Linke A, Bruegel M, Thiery J, Schuler G, *et al.* Regular exercise training compared with percutaneous intervention leads to a reduction on inflammatory markers and cardiovascular events in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* 2008;15:107-12.
26. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A. Exercise Training Intervention After Coronary Angioplasty: The ETICA Trial. *J Am Coll Cardiol.* 2001;37: 1891-900.
27. Hung RK, Al-Mallah MH, McEvoy JW, Whelton SP, Blumenthal RS, Nasir K, *et al.* Prognostic value of exercise capacity in patients with coronary artery disease: the FIT (Henry Ford ExercIse Testing) project. *Mayo Clin Proc.* 2014;89:1644-54.
28. Stewart RAH, Szalewska D, She L, Lee KL, Drazner MH, Lubiszewska B, *et al.* Exercise capacity and mortality in patients with ischemic left ventricular dysfunction randomized to coronary artery bypass surgery or medical therapy - an analysis from the STICH trial (Surgical Treatment for Ischemic Heart Failure). *J Am Coll Cardiol HF.* 2014;2:335-43.
29. Drexler H. Skeletal muscle failure in heart failure. *Circulation.* 1992;85:1621-3.
30. Coats AJS, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, *et al.* Controlled trial of physical training in chronic heart failure – exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation.* 1992;85:2119-31.
31. Hambrecht R, Fiehn E, Weigl C, Gielen S, Haman C, Kaiser R, *et al.* Regular physical exercise corrects endothelial function and improves exercise capacity in patients with chronic heart failure. *Circulation.* 1998;98:2709-15.
32. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consuption for optimal training of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778-86.
33. 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.
34. Lavie CJ, Milani RV, Mehra MR. Peak exercise oxygen pulse and prognosis in chronic heart failure. *Am J Cardiol.* 2004;93:588-93.
35. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, *et al*. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure – a randomized trial. *JAMA.* 2000;283:3095-101.
36. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure – results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation.* 2003;108:554-9.
37. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* 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. *Eur Heart J.* 2012;33:1787-847.
38. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2002;136:493-503.
39. Artero EG, Lee D, Blair SN, *et al.* A prospective study of muscular strength and all-cause mortality in men with hypertension. *J Am Coll Cardiol.* 2011;57:1831-7.
40. Ronda MUPB, Alves MJNN, Braga AMFW, *et al*. Postexercise blood pressure reduction in elderly hypertensive patients. *J Am Coll Cardiol.* 2002;39:676-82.
41. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation.* 2003;107:2435-9.