Trends in Cardiovascular Medicine 25 (2015) 529–536

Available online at www.sciencedirect.com

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What do we know about the cardiac benefits of exercise?

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ABSTRACT

Exercise has long been considered an essential element for sustaining cardiovascular health. A vast literature of clinical studies suggests that exercise serves as an effective intervention for the primary and secondary prevention of cardiovascular disease, although the optimal nature, intensity, and duration of exercise for maximizing these cardiovascular benefits remain unclear. On a molecular level, exercise induces physiologic growth of the heart primarily by driving cardiomyocyte hypertrophy, notably through the interconnected IGF-1–PI3K–AKT1 and C/EBPβ–CITED4 pathways. Here, we explore the range of clinical evidence supporting the cardiovascular benefits of exercise and outline the molecular pathways that play major roles in regulating these protective effects.

Introduction

For thousands of years, exercise has been thought to play an important role in maintaining one's health. In particular, exercise is believed to be a cheap and effective intervention for the prevention and treatment of heart disease. However, it was not until 1953 that the first scientific study was published describing the potential benefits of exercise on cardiovascular health. In this study, Morris et al. [1] discovered that streetcar conductors and postmen in London have lower rates of coronary heart disease and overall mortality than streetcar drivers and desk-based civil servants, respectively. It was hypothesized that these differences were consequences of the greater physical exertion required of conductors who walked the double-decker buses collecting tickets and active postmen who walked around the city delivering mail compared to that of the sedentary drivers and desk-workers. Although there might have been confounding factors that were not fully controlled for in this study, such as the considerable stress of driving in London traffic or working as a civil servant, many subsequent clinical trials and epidemiological studies have confirmed the benefits of habitual physical activity in preventing cardiovascular disease. Paralleling these clinical findings, recent laboratory studies have delineated several molecular pathways that may play important roles in modulating these clinical phenotypes. In this review, we will first describe the effects of exercise on primary and secondary cardiovascular disease prevention, followed by a brief examination of the main molecular pathways involved in regulating the exercise phenotype, and conclude with the therapeutic implications of this research and the directions in which we believe this field will be heading in the near future.

The authors have indicated there are no conflicts of interest.

No primary experimental data are reported in this review. However, all prior studies conducted by the authors were performed after review by the appropriate institutional animal or human studies committee in accordance with the highest ethical standards.

This research was supported by grants from the NIH, USA: [A.R. (R21HL114352, 1UH2TR000901, R01HL110733, and R01HL122987), X.L.(T32HL073734)]. X.W. was supported by the Harvard College Research Program and the Herchel Smith-Harvard Research Fellowship. A.R. is a principal faculty member of the Harvard Stem Cell Institute.

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http://dx.doi.org/10.1016/j.tcm.2014.12.014

Clinical benefits of exercise

Most of the evidence regarding the association between exercise and primary cardiovascular disease prevention comes from observational epidemiological studies (Table). In part, this reflects the logistical challenges that would be associated with conducting a sufficiently powered primary prevention trial of exercise and the difficulty in ensuring long-term adherence to such an intervention. Nevertheless, the association between habitual exercise and reduced cardiovascular mortality is well documented. An early study found that physical fitness is an excellent predictor of cardiovascular mortality, with lower levels of physical fitness correlating with higher mortality risk from cardiovascular diseases in clinically healthy males [2]. A subsequent study not only confirmed this, but also suggested that even moderate levels of fitness may be able to protect both males and females against the influence of other adverse risk factors for mortality, including smoking and hypertension [3]. Although the distinction is not always made clear, lack of exercise and a sedentary lifestyle appear to be separable risk factors for cardiovascular disease, as shown in various prospective studies [4]. Additionally, low levels of exercise and high sedentary time independently increase the risk of heart failure (HF), even after controlling for socioeconomic, clinical, and other lifestyle risk factors [5]. Although these studies are consistent with the hypothesis that exercise—or physical activity more generally—reduces the risk of a range of cardiovascular diseases, they obviously cannot establish a causal relationship. Since subjects in these observational studies self-select to exercise or not, it remains possible that they do so on the basis of genetic or other differences that are actually the causes for their reduction in adverse cardiovascular outcomes. Moreover, residual unrecognized confounding is always a possibility in observational studies, and exercise is likely a marker for other healthy behaviors. Thus, although an important role for exercise in the primary prevention of cardiovascular disease is plausible and intuitively appealing, it is hard to assert with certainty.

Interventional trials are more feasible for secondary prevention. A large randomized controlled trial (RCT) HF-ACTION showed that for HF patients, exercise training resulted in significantly improved self-reported health status and moderate reductions in several clinical end points, including all-cause mortality or hospitalization, significant when adjusted for highly prognostic predictors of the primary end points [6]. Similarly, the GOSPEL study, a multicenter RCT in Italy, showed that a lifestyle intervention that included exercise after myocardial infarction (MI) led to no significant changes in the primary end points such as cardiovascular mortality, nonfatal MI, or hospitalization for heart failure but moderately significant reductions in several secondary end points, including nonfatal MI, cardiovascular mortality plus nonfatal MI, and cardiovascular mortality plus nonfatal MI and stroke [7]. It is uncertain whether the lack of the clear-cut survival benefit in RCTs reflects an inadequate exercise regimen or statistical power, imperfect adherence, or the inability of exercise to mitigate mortality in these settings.

To overcome the statistical limitations of small trials, there have been numerous meta-analyses of RCTs that assessed the effects of exercise (Table). One study found that aerobic exercise training reduced adverse left ventricular remodeling in HF patients, supplemental to established pharmacological treatment, while strength training showed no demonstrable benefit [8]. A meta-analysis of 34 RCTs found that exercise-based cardiac rehabilitation after MI was associated with reductions in mortality and rates of reinfarction, with even relatively short-term exercise-based cardiac rehabilitation protocols potentially translating into long-term benefits [9]. A common worry among patients with established cardiovascular disease is whether the stress of exercise will cause further damage to their heart. Results from the ExTraMATCH collaborative meta-analysis found that properly supervised exercise training programs for HF patients are not dangerous but may actually reduce overall mortality [10].

The secondary preventative effects of exercise are also prominent in other relevant disease populations. A meta-analysis of RCTs involving diabetes patients found that exercise reduces the risk of cardiovascular disease in these patients [11]. Similarly, a prospective study found that in adults with hypertension, higher levels of cardiorespiratory fitness might be able to offset the mortality risk associated with higher adiposity [12]. Most interestingly, a recent meta-epidemiological study suggested that the mortality benefit of exercise in coronary heart disease or prediabetes patients was not statistically different from that seen with established drug interventions [13]. Even more strikingly, the authors claimed that among stroke patients, exercise interventions were more effective at reducing mortality than drug treatments such as anticoagulants and antiplatelet agents [13], although one suspects that other end points (e.g., recurrent stroke) might more readily have revealed differences. Regardless of whether these statements can be proven in randomized controlled trials, a wealth of current clinical evidence drawn from observational studies, RCTs, and meta-analyses supports the concept that exercise is indeed an effective intervention for the prevention of many diseases, cardiovascular and otherwise.

Given this, the American Heart Association (AHA), in conjunction with the American College of Cardiology (ACC), recommends that healthy adults engage in moderate-intensity cardiorespiratory exercise training for at least 30 minutes per day, five days per week, for a total of 150 minutes per week. However, a strong evidence base supporting these—or any other—specific recommendations is generally lacking. In addition to the challenges of demonstrating unequivocally the health benefits of exercise discussed above, there is even less data available to define the optimal nature, intensity, and duration of exercise regimens to achieve these benefits [14]. Interestingly, a recent observational study suggested that even running at moderate speeds for an average of five minutes a day was associated with reductions in cardiovascular and all-cause mortality, with no clear additional benefit associated with greater running duration or intensity [15].

As with most physiologic stimuli, exercise may become deleterious if practiced at excessive levels. The incidence of cardiac arrest is three to five times more likely during