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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/EBP β -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.* discovered that street car conductors and postmen in London have lower rates of coronary heart disease and overall mortality than street car drivers and desk-based civil servants, respectively [1]. 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

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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 which we believe this field will be heading in the near future.

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 as well as 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 socio-economic, 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 endpoints, 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 endpoints, 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 than drug treatment such as anticoagulants and antiplatelet agents at reducing mortality [13], although one suspects that other endpoints (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, 5 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 are 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-causes 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 marathons compared to half-marathons [16]. Several studies of elite athletes have also found that prolonged, excessive endurance exercise can be associated with maladaptive cardiac phenotypes including fibrosis [17], adverse left ventricular remodeling [18] and atrial

fibrillation [19, 20], although confounding or even reverse causality (subjects with concerns about their cardiovascular health may take up extreme exercise in some cases) cannot be fully excluded. For atrial fibrillation, animal studies provide additional support for the hypothesis that prolonged exercise can lead to increased fibrosis, diastolic dysfunction, and atrial fibrillation [21, 22], at least partially driven by angiotensin II activation [23]. For post-MI patients, while increasing exercise generally reduces further cardiovascular disease-related mortality, excessive exercise (running >7.1 km/day or briskly walking >10.7 km/day) may be associated with increased cardiovascular disease-related mortality [24]. It seems likely that exercise should be practiced in moderation to maximize its cardiovascular and systemic benefits, although the precise boundaries are poorly defined and may vary among individuals.

Molecular Mechanisms

The plasticity of the heart allows for adaptations to the increases in cardiopulmonary demand imposed by exercise. These adaptations include left ventricular hypertrophy and improved Ca^{2+} handling, which improves cardiac function. Systemically, vascular changes, such as angiogenesis, and metabolic changes, including improved insulin sensitivity and metabolism, help the heart and body maintain metabolic homeostasis and reduce the risks of cardiovascular diseases. The following reviews provide more thorough examinations of the phenotypic adaptations that promote the clinical benefits of exercise [25, 26]. Here, we will focus primarily on the molecular mechanisms that underlie these phenotypic changes.

In response to the increased cardiac demand of endurance exercise, the heart undergoes physiologic remodeling and hypertrophy. While physiological cardiac hypertrophy due to exercise and pathological cardiac hypertrophy due to hypertension or aortic stenosis are difficult to distinguish clinically, recent studies have shown that exercise and other physiological stimuli induce a transcriptional network distinct from that seen with pathological stimuli [27]. Additionally, although some have suggested that the distinctions between physiological and pathological cardiac hypertrophy are simply due to the intermittent nature of the pressure overload on the heart by physiological stimuli, compared to the more persistent stress by pathological stimuli, an interesting study found that applying intermittent pathological pressure to the heart results in a milder, but nevertheless pathological hypertrophic response [28]. Furthermore, while exercise-induced physiological cardiac hypertrophy is typically accompanied by proportional increases in the length and width of cardiomyocytes, pathological cardiac hypertrophy often shows disproportionate increases in cardiomyocyte length. Taken together these studies support the hypothesis that physiological and pathological cardiac hypertrophy are mechanistically distinct processes even at a stage when the hearts are structurally and functionally indistinguishable.

Exercise-induced physiological cardiac growth may reflect a combination of cellular hypertrophy and hyperplasia. An intensive swimming protocol in mice can induce up to a 45% increase in the cardiomyocyte size in as little as two weeks, and it seems likely that changes in cardiomyocyte size are the dominant contributor to overall physiological heart growth, particularly over short periods of time [27]. However, exercise induces proliferation of at least some cell types in the heart, such as endothelial cells. Intriguingly, recent work by

our group and others has suggested that exercise increases markers of proliferation in cardiomyocytes, once thought to be stagnant and terminally differentiated after maturation. Independent work now suggests that cardiomyocyte renewal does occur naturally at low levels in the adult heart in both animals and humans [29, 30] but little is known about the physiological regulators of this process. We found that exercise increases markers of proliferation in the cardiomyocyte lineage, and identified a transcriptional pathway that appears to mediate this effect (Figure). This pathway works through the CCAAT/enhancer-binding protein β (C/EBP β) [27] and CITED4 (CBP/p300-Interacting Transactivators with E (glutamic acid)/D (aspartic acid)-rich-carboxylterminal domain [31]). Cardiac C/EBP β decreases with exercise, and genetically mimicking this change *in vivo* recapitulates many of the phenotypes seen in exercised hearts and protects mice from transverse aortic constriction (TAC)-induced heart failure [27]. CITED4 increases in exercised hearts (or with genetic reduction in C/EBP β). In neonatal rat cardiomyocytes (NRVMs) *in vitro*, CITED4 is necessary and sufficient for proliferation [27], although neonatal cardiomyocytes are known to retain more capacity for proliferation than adult cardiomyocytes. Of note, the increase in proliferation markers seen *in vivo* is specifically in cells expressing cardiomyocyte sarcomere proteins, which could be cardiomyocytes or committed cardiac progenitor cells (CPC), which appear to express sarcomere proteins at some stages of development [32]. Consistent with the latter model, a subsequent study suggests that exercise training increases the number of putative cardiac progenitor cells in the c-kit^{POS} or Sca-1^{POS} lineages, giving rise to new cardiomyocytes [33]. However, it is important to note that none of these studies can prove that exercise drives cardiomyocyte proliferation *in vivo*. Unambiguously identifying the source and fate of any new cardiomyocytes formed, as well as whether these cells survive and functionally integrate into the myocardium, is of great interest but will require long-term fate-mapping experiments to address.

Interestingly, exercise has been reported to drive cellular proliferation and a potentially regenerative response in multiple other tissues. Like the heart, the brain was once thought to be terminally differentiated and incapable of generating new neurons after early development. However, multiple studies have now shown that exercise can stimulate neurogenesis and cellular proliferation in the dentate gyrus region of the brain [34]. Similarly, exercise was found to induce an increase in the number of hematopoietic stem cells in the bone marrow [35] and to cause proliferation of myogenic stem cells in skeletal muscle [36]. Taken together, these data suggest that exercise induces a proliferative and potentially regenerative response by providing fundamental inductive signals that are conserved across multiple cell lineages. We believe that identifying and learning to exploit these signals holds great promise for regenerative medicine in multiple contexts.

Some of the molecular signals mediating the benefits of exercise have already been identified. Exercise training has a demonstrable cardioprotective effect, reducing cardiomyocyte apoptosis after an ischemic insult [37]. Exercise also offsets the age-induced increase in Bax/Bcl2a ratios, leading to a reduction in cardiomyocyte apoptosis and cardiac remodeling in aging rats [38]. In addition to alterations in pro- and anti-apoptotic Bcl-family member ratios, many effects of exercise are mediated by the IGF-1 or neuregulin-1 (NRG-1) activation of PI3K-AKT1 signaling pathway (Figure). Physiological cardiac hypertrophy

can be induced by IGF-1 administration, which also protects the heart against myocardial ischemia-reperfusion injury [39]. On a molecular level, IGF-1 binds to its tyrosine-kinase receptor, IGF1-R, which activates the p110 α subunit of phosphoinositide-3 kinase (PI3K). PI3K (p110 α) is necessary and sufficient for the induction of physiological hypertrophy [40], and also protects the heart against MI- or TAC-induced HF [41]. Exercise-induced activation of IGF-1 and PI3K then leads to the activation of the serine-threonine kinase, AKT1 (V-akt murine thymoma viral oncogene homolog 1), which is also necessary [42] and sufficient for physiological cardiac growth. In contrast, inhibition of PI3K (p110 α) does not affect pathological hypertrophy due to pressure overload [40] and genetic deletion of AKT1 in fact accelerates pathological hypertrophy in this setting, suggesting AKT1 actually inhibits pathological cardiac growth after TAC [42]. Of note, AKT1 expression in cardiomyocytes also downregulates C/EBP β expression which, as noted above, is sufficient to recapitulate a number of exercise-induced cardiac phenotypes [27].

Endurance exercise also plays an important role in the induction of blood vessels in the heart needed to support the increased metabolic demands and cardiac growth. Exercise induces the release of circulating catecholamines, such as epinephrine and norepinephrine, which targets beta-adrenergic receptors, activating endothelial nitric oxide synthase (eNOS). The activated eNOS releases nitric oxide (NO) into the blood stream, which helps to modulate vascular tone, smooth muscle proliferation, angiogenesis, and reduces myocardial fibrosis. NO homeostasis plays a crucial role in regulating the cardioprotective effects of exercise, particularly against damages caused by ischemia-reperfusion injury [43]. Interestingly, AKT1 also promotes activation of eNOS through phosphorylation [44].

MicroRNAs

Recent studies suggest that microRNAs (miRNAs, miRs) are major regulators of gene expression in the heart. MiRNAs are short ~22 nucleotide strands of non-coding RNA that bind to the 3' or 5' untranslated region (UTR) of their target genes and downregulate the protein expression of these target genes. MiRNAs play significant roles in cardiac pathophysiology [45], cardiovascular development [46], and cardiac regeneration [47]. Several studies have begun to characterize the regulation and role of miRNAs in the exercised heart. A recent investigation profiled the global expression pattern of cardiac miRNAs in physiological left ventricular hypertrophy [48]. A mechanistic study found that aerobic exercise could increase levels of miR-29 in the heart, suppressing collagen gene expression and leading to improved ventricular compliance and other beneficial cardiac effects [49]. Interestingly, exercise alters miRNAs that regulate the PI3K-AKT1 pathway, helping to drive the exercise-induced physiological cardiac response [50].

Circulating miRNAs may also be particularly relevant to the physiological exercise response. These miRNAs are secreted or released from cells into the plasma of an animal and may serve important roles in intercellular communication, potentially regulating both the cells that release them and the cells that take them up. We believe circulating miRNAs may be especially intriguing in the exercise response because they could potentially help drive similar phenotypes, such as cellular proliferation, across multiple organ systems. Of particular interest are miRNAs circulating in exosomes, which pass through the blood-brain-

barrier under certain conditions, and could in theory transmit exercise-induced signals contributing to the beneficial effects of exercise on the brain. Circulating miRNAs may also serve as clinically useful biomarkers for cardiovascular fitness and/or risk, due to their stability and specificity [51]. As an example, miR 423-5p was recently reported as a circulating biomarker for heart failure [52].

Recent efforts have tried to profile changes in circulating miRNAs in response to aerobic exercise in humans and found distinct circulating miRNA signatures following acute and sustained exercise [53, 54]. Additional human studies assessed the distinct changes in circulating miRNA levels under various exercise modalities [55], and also examined the unique temporal dynamic regulation of specific circulating miRNAs after prolonged exercise [56]. These studies may help identify potential biomarkers for assessing levels of cardiovascular fitness in patients, paving the way for more targeted counseling and personalized treatments for heart disease patients in the clinic. More studies will be needed to validate not only the precise profile of circulating miRNAs after exercise but also to investigate their functional roles.

MiRNAs also have the potential to be exploited for therapeutic purposes. Recently, modified nucleotides such as locked-nucleic acid (LNA) miRNA inhibitors (*antimiRs*) and agonists (*agomiRs*) have been developed for use *in vivo* models and early-phase clinical trials. LNA-antimiRs have been used to treat HCV infection by downregulating miR-122 in clinical trials and appeared to be generally well-tolerated [57]. Another study found that miR-214 agomiR targeting ATF4 could inhibit bone formation [58]. These studies and many others highlight the therapeutic potential of miRNAs to treat disease. By identifying miRNAs that contribute to the benefits of exercise, we may one day be able to manipulate these miRNAs in the clinic to restore cardiovascular health to patients with heart disease.

Future directions

Since much is still unknown about the mechanisms underlying the exercise-induced physiologic changes in the heart, there are numerous research directions that will be interesting to pursue. Now that we are beginning to clinically distinguish the risks associated with a sedentary life-style and lack of habitual exercise, it would be interesting to assess whether there may be distinct molecular pathways that modulate these processes. Furthermore, a more precise understanding of the time and intensity-response of exercise, as well as the mechanisms that drive these responses, may help us uncover novel, functionally-relevant pathways that play important roles in promoting cardiovascular health and preventing adverse cardiac remodeling. This may be an area of synergy between clinical and animal studies, where it is easier to mandate and maintain exercise protocols. However, extrapolating results from animals to humans is itself non-trivial given differences in species physiology and scale. Undoubtedly, it will also be valuable to more fully characterize the pathways that regulate cardiomyogenesis in the adult heart, and in this context, exercise may provide a useful model of a physiological inductive cue that we hypothesize enhances the endogenous reparative capacity of the heart. While much is known about the roles of miRNAs in regulating pathological or developmental cardiac pathways, we know less about their functional roles in modulating the exercise-induced cardiac response. It would be

interesting to identify miRNAs altered in the heart and plasma by exercise, and elucidate the molecular pathways that are regulated by these miRNAs. In this context, it may also be valuable to compare the miRNA profiles of exercised human and animals, in order to help develop appropriate and applicable animal models to elucidate the molecular mechanisms underlying their function in exercise. Ultimately, understanding the mechanisms that these miRNAs play in the physiologic exercise response may lead to the development of miRNA therapies that can help prevent primary and secondary onset of cardiovascular diseases and restore heart health to patients. Lastly, another fascinating area of exploration may be to assess the role of exercise in modulating the physiological responses of aging. While much has been suggested regarding the potential anti-aging effects of exercise, very little is known about the molecular mechanisms linking exercise and aging. A clearer understanding of this relationship on a basic science level may lead to the identification of novel therapeutic targets, which could one day help to stall or reverse the adverse effects of aging and aging-related diseases.

Why should we care?

Physical inactivity is a major risk factor for disease burden worldwide. A wealth of clinical data suggest that exercise is one of the cheapest and most effective interventions for promoting cardiovascular health, so those who can safely exercise should. However, not everyone is physically capable of exercising and ironically those most in need (e.g. those with established cardiovascular disease) are often those for whom exercise training is most challenging. It is worth remembering (and reminding our patients) that even modest levels of physical activity are associated with considerable health benefits. Nevertheless, elucidation of the molecular mechanisms mediating the protective effects of exercise may lead to the identification of novel biomarkers and/or therapeutic targets, not previously gleaned from complementary studies of disease. It is also possible that small molecules or biological interventions aimed at these targets could optimize specific aspects of the cardiovascular exercise response in a way difficult or impossible to achieve through exercise, although we are skeptical that any drug intervention or “exercise mimetic” will fully recapitulate the myriad benefits of habitual physical activity.

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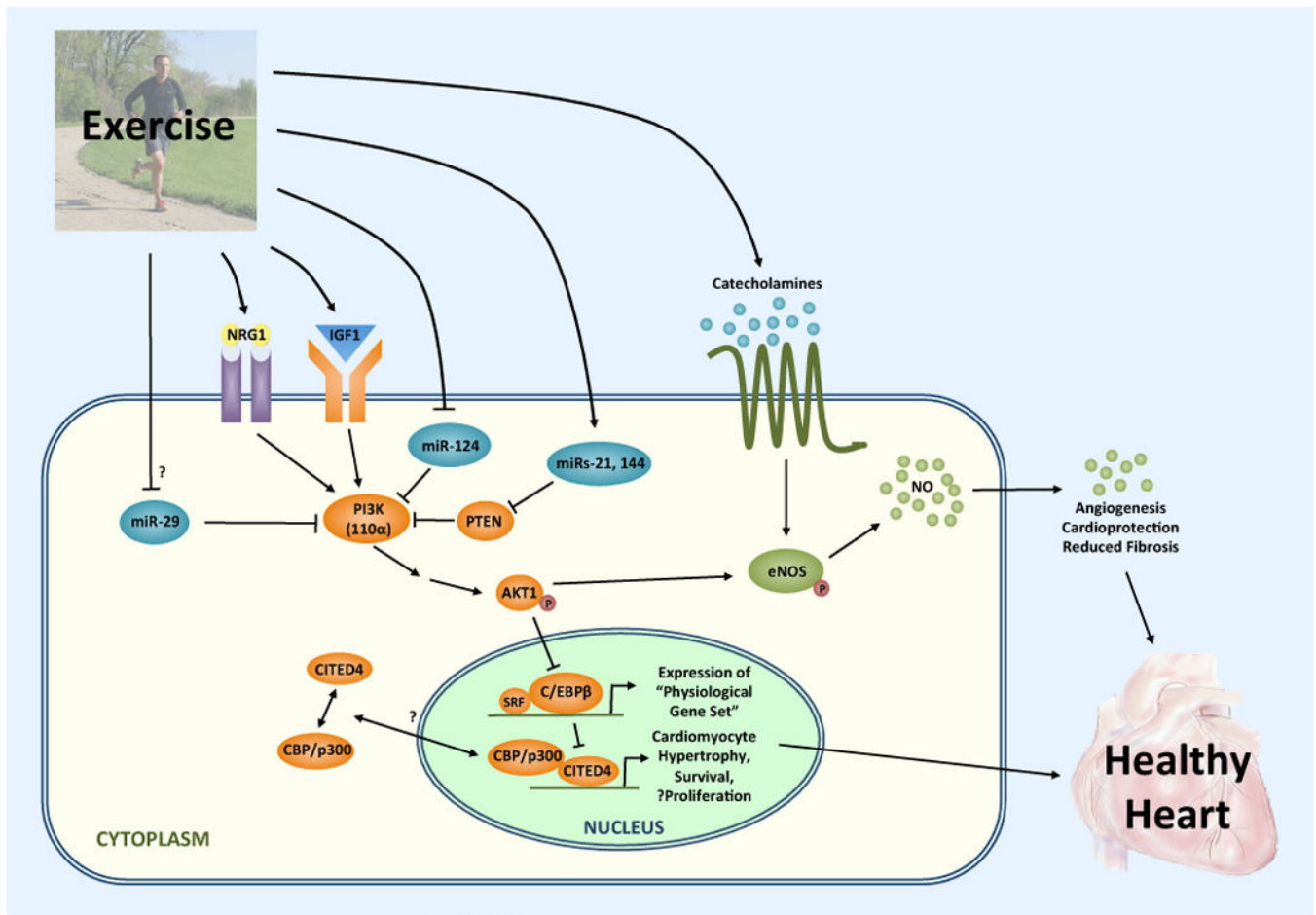


Figure. Representative molecular pathways contributing to the cardiac exercise phenotype

Exercise increases both IGF-1 and neuregulin (NRG-1), activating the PI3K-AKT1 pathway, which in turn inhibits the transcription factor C/EBP β in the nucleus. Downregulation of C/EBP β activates the expression of a physiological gene set that drives cardiac growth by cardiomyocyte hypertrophy and proliferation, including upregulation of CITED4. CITED4 binds CBP/p300, either in the cytoplasm or nucleus, and also activates genes involved in cardiomyocyte growth and proliferation. Moreover, exercise leads to the differential expression of specific miRNAs, including some that are upregulated (e.g. miR-21 and miR-144) and others that are downregulated (e.g. miR-124 and potentially miR-29), that target and help regulate various components of IGF-1-PI3K-AKT1 signaling among other pathways. Lastly, exercise-induced release of catecholamines and activation of AKT1 concurrently mediate angiogenesis and other protective vascular remodeling via activation of eNOS.

Table

Study/Reference	Primary or Secondary Prevention	Study type	Population Studied	Sample Size/ Number of Studies	Significant Conclusions
Morris, JN et al. (1953)	Primary	Observational	Bus conductors/drivers, Postmen/Civil servants	31,000 Subjects	Bus conductors and postmen have lower rates of CHD and overall mortality than bus drivers and desk-based civil servants, respectively.
Ekelund, LG et al. (1988)	Primary	Observational	All Men	4276 Subjects	Low levels of physical fitness is correlated with a high mortality risk for CHD and CVD
Blair, SN et al. (1996)	Primary	Observational	All Adults	32,421 Subjects	Low levels of fitness is a precursor of CVD and all-cause mortality; moderate levels of fitness can protect against other risk factors of premature mortality.
Proper, KI et al. (2011)	Primary	Review	All Adults	19 Studies	Sedentary behavior is associated with a higher risk of CVD, independently of levels of exercise.
Young, DR et al. (2014)	Primary	Observational	All Men	82,695 Subjects	Low physical activity and sedentary behavior are independently correlated with increased risk of heart failure
Lee, DC et al. (2014)	Primary	Observational	All Adults	55,137 Subjects	Running for as little as an average of five minutes a day is associated with a reduction in CVD and all-cause mortality.
O'Connor, CM et al. (2009)	Secondary	RCT	Heart Failure Patient	2,331 Patients	Randomized trial in heart failure patients demonstrating that exercise training reduces all-cause mortality or hospitalization and cardiovascular mortality, or heart failure hospitalization, when adjusted for baseline differences in prognostic predictors of mortality.
Giannuzzi, P et al (2008)	Secondary	RCT	Post-MI Patients	3,241 Patients	Overall life-style intervention (including exercise training) reduces nonfatal myocardial reinfarction
Haykowsky, MJ et al. (2007)	Secondary	Meta-Analysis	Heart Failure Patients	14 RCTs	Exercise training reduces adverse LV remodeling and improves EF, EDV and ESV
Lawler, PR et al. (2007)	Secondary	Meta-Analysis	Post-MI Patients	34 RCTs	Exercise-based cardiac rehabilitation reduces the risk of reinfarction, CVD and all-cause mortality
Piepoli, MF et al. (2004)	Secondary	Meta-Analysis	Heart Failure Patients	9 RCTs	Exercise training programs for HF patients is not dangerous, but reduce overall mortality
Kodama, S et al (2013)	Secondary	Meta-Analysis	Diabetes Patients	17 RCTs	Exercise reduces risk of all-cause mortality and CVD
McAuley, PA et al (2009)	Secondary	Observational	Men with Hypertension	13,155 Subjects	Exercise may offset the mortality risk associated with higher adiposity
Naci, H et al. (2013)	Secondary	Meta-epidemiological	All Adults	16 Meta-analyses	Mortality benefit of exercise is not statistically different than that of established drug interventions for CHD or pre-diabetes patients, and may be even better than drug interventions for stroke patients