Editorial

Fitness and strength in young adulthood and protection from future heart failure

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We are in the midst of a heart failure (HF) pandemic with wide-ranging implications for aging populations, physicians, and healthcare delivery systems (1). The major epidemiologic determinants for HF have been traditionally viewed as hypertension, coronary artery disease, valvular disease, and more recently obesity, diabetes, and kidney disease (2,3). Among those with HF, approximately half have HF with reduced ejection fraction (HFrEF) and the other half with preserved ejection fraction (HFpEF). In this issue of the *European Journal of Preventive Cardiology*, Lindgren and co-workers report on a ray of hope in HF epidemiology (4). They describe a protective relationship between cardiopulmonary fitness as well as muscle strength and the development of HF at a relatively young age in all categories in which it can be accounted for using automated sources of data. This report is a major advance in the cardiopulmonary fitness literature, which has had a global interest in "survival of the fittest" which was a way of explaining the relationship between fitness and mortality (5). In brief, cardiopulmonary fitness has been associated with reduced mortality not only because of improved risk factors, and modest reductions in atherosclerotic events such as myocardial infarction, but because it markedly improves the survival of potentially fatal events such as critical illness.

In the present study, the highest group of cardiopulmonary fitness (42.2% of men) was associated with a 49%, reduction in the incidence of HF after adjusting for important confounders such as age, hypertension, diabetes, congenital heart disease, alcohol abuse and measured blood pressure (model 2) (4). Likewise, in the same model, the highest muscular strength (31.3% of men) conferred a 50% reduction in HF. The two measures had collinearity so when considered together, adjustment bias reduced the risk relationships, but does not take away from the key findings: fitness in young adulthood is associated with sharply lower rates of HF decades later.

Given the very large sample size and the internal consistency of the data, we believe the relationships reported are valid. This accepted, one must consider an array of mechanisms with the understanding that there is a large gap in time between the fitness measurements and the outcome of HF, which occurred at a young age given the time window available in the data. While at age 18 the body mass index was 22 kg/m^2, none of the fitness groups appeared to be on a significant obesity trajectory at this snapshot in time (6). It is possible that the lower fitness and strength men, with lower measures of intellectual capacity, were more likely to be on a pathway towards obesity, hypertension, diabetes, and poorer health status. If exercise patterns persisted several years or decades into life, then the cardiometabolic effects could have clearly played a role. A recent analysis from the Multi-Ethnic Study of Atherosclerosis and Cardiovascular Health Study found that voluntary, leisure time physical activity in earlier life was associated with an adjusted ~25% reduction in the risk of future HF (7). The protective effect appeared to be more pronounced for HFpEF. It is known that exercise decreases body weight, improves lipids (decreasing triglycerides

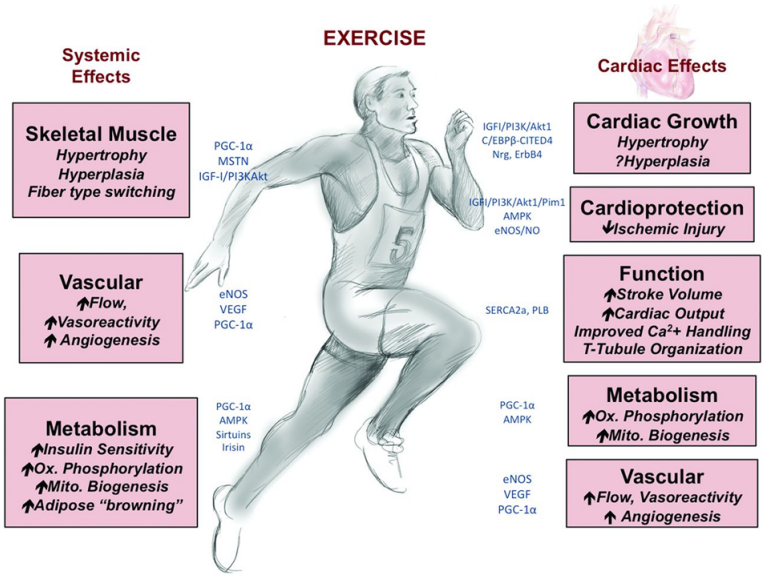

Figure 1 Cardiovascular effects of exercise and potential pathways for skeletal and myocardial adaptation that could be protective in the development of heart failure by activating a gene set with an array of protein products. AMPK indicates AMP-activated kinase; C/EBPβ, CCAAT/enhancer binding proteinβ; CITED4, cbp/p300-interacting transactivator with Glu/Asprich carboxy-terminal domain 4; eNOS, endothelial nitric oxide synthase; IGF-1, insulin-like growth factor-1; MSTN, myostatin; Nrg1, neuregulin1; PGC-1, peroxisome proliferator activated receptor gamma co-activator 1; PI3K, phosphoinositide kinase-3; Pim1, proto-oncogene serine/threonine-protein kinase-1; PLB, phospholamban; SERCA2a, sarco/endoplasmic reticulum Ca^{2+}-ATPase, 2a; and VEGF, vascular endothelial growth factor. Reproduced with permission from reference (12).

and increasing high-density lipoprotein cholesterol) and improves insulin resistance (decreasing fasting insulin and hemoglobin A1C). Exercise has also been shown to decrease levels of interleukin-18 and lower levels of leptin, fibrinogen, and angiotensin II. Individuals with type 2 diabetes, hypertension, dyslipidemia, or metabolic syndrome benefit more from exercise (8). Accordingly, cardiopulmonary fitness is inversely associated with fasting serum insulin, waist-to-hip ratio, and coronary heart disease (9). Obesity is associated with cardiac adiposity, characterized by the accumulation of triglyceride in the myocardium and also deposition of fat around the heart and vessels, which may lead to left ventricular hypertrophy and dysfunction. This lipid accumulation is associated with the release of proinflammatory and proatherogenic cytokines resulting in systemic or local inflammation (10). Thus obesity is clearly related to the development of HFrEF and to a greater extent for HFpEF. A reduction in the risk HF-related death may be an explanation of how cardiorespiratory fitness is broadly associated with reduced mortality among all weight groups (11). The authors may be able to further evaluate this "cardiometabolic" hypothesis by reporting BMI, hypertension, and diabetes at the time of the index hospitalization and indicate whether HF cases are HFpEF or HFrEF.

Another potential mechanism is more directly focused on the myocardium itself. It is possible cardiopulmonary fitness as reflected by peak oxygen consumption in mL/kg/min has a legacy effect in life. Simply said, stronger hearts at younger ages may remain stronger than average over the course of time and be protected from the development of HF due to an array of etiologies. Fitness and strength in young adulthood may be related to a greater proclivity towards more leisure time physical activity in later life (7). As shown in *Figure 1* there is an exercise "gene set" that is activated with exercise and results in fundamental changes in cardiomyocyte development and growth, performance, and potentially long-term organ function involving an array of cellular and tissue factors (12). Exercise induces cardiac expression of insulin-like growth factor-1, which activates the PI3K-Akt cascade resulting in cardiomyocyte hypertrophy. Simultaneous inhibition of the transcription factor C/EBPβ contributes to activation of an exercise gene set (cardiac specific transcription regulators GATA 4,

alfa-MHC, Mef2C) which results in expression of many structural proteins enabling cell growth and differentiation (13). Exercise upregulates sirtuins 1 and 3 (Sirt 1 and Sirt3), which are nicotinamide adenine dinucleotide-dependent deacetylases and that regulate cellular metabolism, cell growth, apoptosis, and aging. Sirt1 has pro-growth and pro-survival functions in cardiomyocytes. Sirt3 protects against oxidative stress and regulates the opening of the mitochondrial permeability transition pore, which appears to be protective against age-related cardiac dysfunction. These are among many cellular changes that occur within cardiomyocytes in response to exercise. Activation and maintenance of an exercise gene set would explain why the data were so consistent across categories of HF that emerged from the codified hospitalization data. This mechanism is worthy of intensive exploration since myocardial energetics, cardiac morphology, hemodynamics, and peripheral vascular adaptation are all known to be different in the athlete compared to the non-athlete (14). The old adage is that fitness is lost quickly with a cessation of training, but perhaps there are special enduring protective effects that are yet to be discovered. The authors may be able to shed more light on this mechanism with greater detail about the index HF hospitalization including the left ventricular ejection fraction and other measures of cardiac function, hemodynamics, and morphology.

In summary, the relationship between fitness in youth and throughout life and protection from the development of HF should be hotly pursued. The mechanisms accounting for protection could lead to future diagnostic and therapeutic targets in both the heart and skeletal muscles (15). From a public health perspective, aerobic and strength conditioning programs could possibly have a large and beneficial impact given the size of the HF epidemic and its leading role in adult non-traumatic hospitalizations worldwide.

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