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Exercise Training for Prevention and Treatment of Heart Failure

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ABSTRACT

Heart failure (HF) results in high healthcare costs and burdens for the United States in respects to hospitalizations, therapies, and associated disability. The relative proportion of HF with preserved ejection fraction (HFpEF) compared with HF with reduced ejection fraction (HFrEF) is on the rise; HFpEF has already become the dominant form of HF and it continues to increase. The serious implications of these trends are compounded by a dearth of effective HFpEF therapies. While low physical activity, low cardiorespiratory fitness (CRF), and obesity, are risk factors for HF in general, they particularly predispose to HFpEF. Thus, weight loss and exercise that leads to improved CRF may constitute important opportunities for effective intervention. In this review, we discuss the interplay between physical inactivity, CRF, and obesity in the development of HF, particularly HFpEF, and highlight the current evidence on weight loss and exercise as preventive and therapeutic opportunities.

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Abbreviations and Acronyms

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

CRF = cardiorespiratory fitness

ET = exercise training

CV = cardiovascular

CVD = cardiovascular disease

CCLS = Cooper Center for Longitudinal Study

LV = left ventricular

PA = physical activity

BMI = body mass index

CARDIA = The Coronary Artery Risk Development in Young Adults Study

QoL = quality of life

CR = cardiac rehabilitation

CMS = Center for Medicare and Medicaid Services

ICD = implantable cardioverter and defibrillator

CHD = coronary heart disease

Heart failure (HF) is a growing epidemic that affects up to 6.5 million Americans and contributes significantly to the increasing burden of health care costs.[1,2] More than 960,000 new cases of HF are diagnosed yearly and the annual cost of care for HF is estimated to be more than 30 billion dollars. Once HF is diagnosed, the survival estimates at 5 years are between 40–50%.[2]

Two distinct phenotypes of HF have been identified: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Prevalence of HF continues to increase, and over the past decade, incidence of HFpEF has surpassed HFrEF.[3] Furthermore, while significant progress has been made in the development of effective therapies against HFrEF, few therapies have proven efficacious in patients with HFpEF. As a result, there is an urgent need for novel approaches to prevention and treatment of HFpEF.[4]

Physical inactivity, low cardiorespiratory fitness (CRF), and obesity have been identified as significant risk factors for HF, particularly HFpEF.[4,5] Furthermore, recent studies have demonstrated that improvement in CRF and weight loss may be associated with lower downstream risk of HF.[6,7] Thus, there is an increasing interest in lifestyle interventions such as exercise training (ET) and intentional weight loss as vital opportunities for prevention. In this review article, we discuss the roles of physical inactivity, low CRF, and obesity as potential targets for primary prevention of overall HF, and particularly HFpEF. We also elaborate on the role of ET and intentional weight loss as effective therapeutic strategies for management of HF and its subtypes.

Physical inactivity, low CRF and risk of HF

Low CRF and physical inactivity have been associated with higher risk of HF incidence in several large cohort studies (Table 1). Recent work from the Cooper Center Longitudinal Study (CCLS) has demonstrated that low CRF (mean METs 8.4 in men, 6.4 in women) levels in mid-life are more strongly associated with higher risk of HF than acute MI in older age.[8] Furthermore, risk of HF associated with low CRF remains independent of other cardiac and non-cardiovascular (CV) disease (CVD) risk factors.[6]

The phenotype of HF associated with low CRF or physical inactivity is less well established, but several reports suggest that these risk factors may be implicated in the development of HFpEF. For example, a cross-sectional analysis from the CCLS demonstrated that low CRF was strongly associated with diastolic filling impairment and higher left ventricular (LV) filling pressure, i.e., risks for HFpEF development.[9] In contrast, no significant association was observed between CRF and LV systolic dysfunction. Similar risk patterns were also observed in a longitudinal analysis from the CARDIA study cohort where low CRF in young adulthood was more strongly associated with subclinical diastolic filling impairments 20 years later, but not systolic dysfunction.[10] Thus, low CRF and HFpEF seem interrelated. Corroborating conclusions were made in a pooled analysis using data from three large cohorts, the Women's Health Initiative, the Cardiovascular Health Study, and the Multiethnic Study of Atherosclerosis.[11] In this study, the authors observed a strong dose dependent association between increasing levels of leisure time physical activity (PA) and risk of HFpEF but not HFrEF.[11] Bhella et al.[12] also completed a mechanistic analysis and showed a strong dose-dependent inverse association between lifetime dose of exercise and LV end-diastolic stiffness, another phenotype for HFpEF.[13]

Obesity and risk of HF

Higher body mass index (BMI) and obesity are well-established risk factors for HF. A recent study level meta-analysis reported a dose dependent association between increasing BMI above the normal range and risk of HF such that every 5 kg/m^2 increase in BMI was associated with a 41% increase in the relative risk of HF.[14]

Recent studies have focused on the risks of high BMI and obesity in relation to HFpEF. In a recent individual level pooled analysis, Pandey et al. demonstrated that increasing BMI had a strong and more dose-dependent association with HFpEF as compared to risk of HFrEF.[11] Similar findings have also been observed in other cohorts.[15] While the dose-dependent association between higher BMI and risk of HFpEF was independent of other CVD risk factors including PA levels, it is unclear if obesity and HFpEF are associated directly. Rather, it seems that differences in CRF may contribute to this association. Consistently, a recent study from the CCLS showed that CRF explained ~50% of higher BMI-associated risk of HF.[16] Future studies are needed with clearly adjudicated standards of HFpEF, CRF, and BMI, to better delineate the relationships between these factors.[17,18]

CRF improvement and weight loss modify downstream risk of HF

Recent studies have evaluated the impact of improved PA, CRF, and weight loss on risk of HF. In a sub-analysis from the CCLS, among middle-aged low fit individuals who had repeat