Heart Metab. (2018) 76:36-39

Exercise and diet for heart disease in the frail patient: fact or fiction?

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Abstract
Frailty represents a state of increased physiological vulnerability and diminished reserve, as well as a complex interaction between age, comorbidities, demographics, and lifestyle. Frailty has repeatedly been demonstrated to be an independent prognostic factor across the spectrum of cardiovascular disease; however, frail patients are often excluded from major clinical trials, leading to a significant gap in the evidence. In this review, we discuss the impact of nutrition and exercise interventions on frailty and, consequently, on cardiovascular disease. ■ *Heart Metab*. 2018;76:36-39

Keywords: frailty; heart disease; lifestyle intervention

Introduction

Over the past decade or so, we have observed a major shift in the nature of the challenges facing cardiovascular clinicians and researchers. Advances in the treatment and prevention of coronary disease have resulted in a diminution in deaths attributable to coronary heart disease. We now live in an aging society, where hypertension remains highly prevalent,[1] heart failure with preserved ejection fraction (HFPEF) is emerging as the most common HF phenotype,[2] and there is a significant increase in nonsurgical percutaneous valve interventions for aortic stenosis. Although age alone cannot be implicated for each of these, it is clear that future developments in the management of cardiovascular disease will be closely intertwined with our understanding of the pathophysiology of cardiovascular aging and its interactions with comorbidities, such as frailty.

The definition of frailty remains challenging; however, at its core, it represents a state of increased vulnerability to external stressors and a decreased physiological reserve. Although the components of frailty are diverse, emerging paradigms include a cycle of immune dysregulation with chronic inflammation, a catabolic state, and progressive sarcopenia, which further contributes to physical inactivity.[3]

Frailty is an independent prognostic factor for both coronary artery disease and heart failure. Within the cardiovascular system,[4] frailty is associated with increased atherosclerosis and coronary calcification, with a reduced vasodilatory capacity, impaired microvascular function, increased arterial stiffness, and increased myocardial fibrosis. Together, these play a major physiological role in the pathogenesis of heart failure. Finally, degenerative diseases of the conducting system and left atrial fibrosis contribute to the

increased prevalence of both bradyarrhythmias and tachyarrhythmias.

Assessing frailty

Frailty has consistently been demonstrated to be a major independent prognostic factor for patients with a variety of cardiovascular diseases, both in the acute and chronic setting and in the periprocedural period. Multiple different scoring systems exist to quantify frailty, with the Fried index[5] being the system most cited in short- and long-term outcome studies, including within cardiovascular disease. The Fried index analyzes five domains (gait speed, weakness, exhaustion, weight loss, and physical inactivity); however, it does not examine cognition or mood. It remains unclear if cognition and mood are part of the pathobiological diagnosis of frailty or if they simply act as a modifier for its impact on quality of life. Of these domains, exercise and dietary counseling, as modifiable factors, can have a significant impact on outcomes.

Treating cardiovascular disease in the elderly

Coronary artery disease

The elderly represent the fastest growing group of patients being referred for cardiac surgery; however, newer interventional and structural techniques have reduced the need for major operative care. Traditionally, predicting outcomes following both percutaneous coronary intervention (PCI) and cardiac surgery have been limited in accuracy in elderly patients, with a tendency to overestimate mortality. In this setting, frailty assessments have demonstrated an independent, incremental benefit in predicting adverse outcomes, particularly concerning gait speed, disability, and quantification of comorbidities.[6] In patients undergoing PCI, frailty was again markedly predictive of mortality, and improved the discrimination of predictive models.[7] Most importantly, the involvement of patients in a dedicated cardiac rehabilitation program improves morbidity and mortality; however, there is a paucity of studies examining frailty that are specifically tailored toward cardiac rehabilitation.

Heart failure

The primary limiting symptom for patients with heart failure is exercise intolerance, measured objectively as peak oxygen consumption at maximal exercise or peak V_{O_2}. Both central and peripheral limitations result in an approximate 35% reduction in peak V_{O_2}, regardless of ejection fraction.[4] It has become increasingly apparent that frailty is a common comorbidity in patients with heart failure, with reduced physical activity leading to sarcopenia, as well as the systemic nature of the disease itself, with direct consequences on the pulmonary and renal systems in particular. Exercise training has demonstrated significant benefit across the spectrum of symptoms and ejection fractions, with a well-established safety profile, although a greater benefit has been seen in patients with heart failure with reduced ejection fraction (HFREF) versus patients with HFPEF. Overall, however, there is a lack of data on guideline-based medical therapy in elderly patients for a multitude of reasons, primarily due to the exclusion of these patients from large-scale clinical trials.

The HF-ACTION trial (Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing),[8] an international, multicenter, controlled trial, randomized 2331 patients to 36 supervised exercise sessions followed by home-based training or usual care. The median age was 59 and 20% of the patients were over the age of 70. These patients had a significantly higher comorbidity score, a lower body mass index, and severe systolic dysfunction (median ejection fraction, 26%). Overall, there was a nonsignificant reduction in the primary end point (a combination of mortality or hospitalization), which became significant after multivariate adjustment. Subgroup analysis revealed no significant difference with age concerning the response to exercise training; importantly, age was the strongest predictor of peak V_{O_2},[9] independent of peak heart rate, which is another significant predictor. This noted, age alone only explained 12% of the variance in peak V_{O_2}, meaning that other peripheral factors that contribute to frailty may be explanatory.

The overall impact of exercise-based rehabilitation on heart failure was elegantly summarized in a 2014 Cochrane review[10] that reviewed 33 randomized controlled trials (n=4740 patients). Both patients with HFREF and HFPEF were included, although data on patients with HFPEF were only present in a portion of the four trials. Overall, there was no difference in the 12-month mortality, even though there was a trend toward a reduction at the long-term (10-year) follow-

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up. At the 12-month follow-up, admission rates were significantly reduced, quality of life was improved, and support for the cost-effectiveness of exercise-based rehabilitation was demonstrated.

Nutrition, frailty, and CVD

Frailty and nutritional status are closely linked. Unintentional weight loss is a key domain of the original Fried criteria, which may occur due to inadequate energy intake, an important modifiable risk factor. Lowered energy intake is commonly seen with increasing age, and it has been associated with the development of frailty, especially when under the threshold of 25 kcal/kg/day.[11] Protein is a critical factor to maintain muscle mass, with up to 15% of patients over the age of 60 demonstrating intake below the recommended dietary allowance.[12] A careful balance must be struck between adequate intake and avoidance of excessive protein load for a delicate renal system. Although patients able to receive at least 25 to 30 grams of protein have evidence of slowed sarcopenia,[13] large randomized trials have not demonstrated the benefit of higher protein intake in frail patients, which may be due, in part, to impaired synthesis of muscle protein in the context of frail muscle, rather than through lowered protein intake alone.

High sodium intake is also strongly correlated with elevated blood pressure, particularly in older adults.[1] In addition to the vitamins B6 and B12, vitamins C[14] and D[15] have both been independently linked with frailty, although a U-shaped curve is noted with the latter. Vitamin D supplementation improves muscle strength and reduces frailty; however, there is conflicting evidence regarding cardiovascular outcomes, with the most recent data suggesting no significant benefit.[16] Other micronutrients have also been implicated, but this requires further evaluation in large-scale randomized trials.

The Mediterranean diet is considered beneficial for patients with cardiovascular disease. A recent systematic review and meta-analysis demonstrated that greater adherence to the diet reduced the risk of frailty, and the consequent impact on cardiovascular disease will require further investigation.

The gut microbiome has recently become the focus of attention, with significant evidence demonstrating a link with hypertension,[17] heart failure, and other forms of cardiovascular disease. Frail older adults have a less diverse microbiome than younger adults,[18] which may potentially provide a key link between aging, frailty, systemic inflammation, and the development of cardiovascular disease.

Conclusions

Frailty is increasingly prevalent in older patients with cardiovascular disease, remains an independent prognostic indicator of outcomes, and it is modifiable through prescriptive exercise and nutritional counseling. Efforts should be made to quantify frailty using validated scales and target the frail patient, regardless of age, with appropriate lifestyle-modifying therapies to reduce cardiovascular morbidity and mortality. It is well recognized that frail patients are often excluded from major research studies; consequently, there is a drive to encourage trialists to include patients of increasing age, to carefully and objectively measure frailty, and to determine the impact of interventions on slowing the progression of frailty or reversing it. ■

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