HIGHLIGHTED TOPIC | Exploring New Concepts in the Management of Heart Failure with Preserved Ejection Fraction: Is Exercise the Key for Improving Treatment?

Exploring new concepts in the management of heart failure with preserved ejection fraction: is exercise the key for improving treatment?

Kerry S. McDonald¹ and Craig A. Emter²

¹Department of Medical Pharmacology and Physiology, University of Missouri-Columbia, Columbia, Missouri; and ²Department of Biomedical Sciences, University of Missouri-Columbia, Columbia, Missouri

APPROXIMATELY 50% OF ALL PATIENTS diagnosed with heart failure (HF) have HF with preserved ejection fraction (HFP EF) (1). Despite having preserved systolic function at rest, these patients display reduced cardiac functional reserve and morbidity/mortality rates similar to values observed in HF patients with reduced systolic function (HFrEF). Although HFP EF has been clinically recognized for over 30 years, our understanding of the disease and approach to treating it remains a mystery. The pathological mechanisms underlying HFP EF and the efficacy of conventional HF treatments in these patients are controversial and poorly understood (11). Indeed, conventional HF treatments have largely failed to improve the prognosis of this HF subgroup (4). Furthermore, a divergence is becoming more apparent regarding the pathology underlying HFP EF vs. those patients exhibiting HFrEF (2). These findings illustrate the critical need for research examining the mechanisms underlying this phenotypical divergence and development of novel treatment strategies for HFP EF patients.

Exercise is an outstanding tool to identify mechanisms underlying cardiovascular function in health and disease, and it holds excellent promise as a treatment option. Previous research, including the recently completed HF-ACTION clinical trial, indicates exercise training is a safe and effective therapeutic modality in the treatment of HFrEF patients. However, a limitation of the HF-ACTION trial was that patients displaying HFP EF were not included. Using exercise clinically in the treatment of HFP EF takes on added significance given conventional HF treatments have failed to improve prognoses in this HF subgroup. Little is known regarding exercise training in HFpEF patients, and a limited number of human and animal studies have been conducted examining exercise training in this disease setting. Consequently, exercise may serve as an effective therapeutic intervention to improve clinical outcomes in HFP EF patients, yet remains underutilized because the mechanisms whereby exercise exerts its beneficial effects remain largely unknown.

The focus of this Journal of Applied Physiology Highlighted Topic is to 1) examine mechanisms currently considered fundamental to the disease process, 2) cover exciting new developments in the therapeutic management of HFP EF, and 3) assess the influence of exercise in fostering new discoveries. Articles will provide novel insight into the treatment and pathology of HFP EF from leading clinicians and basic scientists in humans and animal models. Over the next 3 months, 7 minireviews and several research articles will be published in the Journal of Applied Physiology that we hope will provide “one-stop shopping” regarding current conceptual understanding of the etiology and treatment of HFP EF.

The first month will contain reviews emphasizing clinical approaches to using exercise in the treatment of HFP EF. The first is a systematic review and meta-analysis regarding cardiovascular clinical outcomes in HFP EF patients after chronic exercise training. Dr. Neil Smart and his team (5) provide a comprehensive epidemiological analysis of the most recent clinical trials exploring exercise as a therapeutic option to treat HFP EF. The second review comes from Drs. Satyam Sarma and Ben Levine (10), who explore exercise oxygen kinetics in HFP EF. Skeletal muscle oxygen delivery and utilization has been shown to be impaired in HFP EF patients, and their analysis explores how specific exercise programs may improve peripheral efficiency and subsequent aerobic performance. In the third review, a group led by Drs. Mark Haykowsky and Dalane Kitzman (6) examine mechanisms underlying exercise intolerance in HFP EF patients. Both central and peripheral impairments play an important role in the reduced cardiac reserve observed in HFP EF, and these limitations to exercise capacity are presented as novel therapeutic options.

In the second month, the focus shifts to the coronary vasculature and a thorough examination of its mechanistic role in developing heart failure. The initial offering comes from a collaboration headed by Drs. Daphne Merkus and Dirk Duncker (7) that provides a unique perspective on the heart’s vascular response to acute exercise in both HFP EF and HFrEF. A number of concepts are outlined and discussed in reference to the regulation of coronary blood flow during acute exercise and how chronic exercise training may be used to treat cardiovascular dysfunction in a setting of heart failure. Second, a recent paradigm has implicated the coronary endothelium as a primary mechanism driving the development of HFP EF (9). Dr. Li Zuo and his colleagues (12) review the research surrounding this concept and examine the integrative influence of reactive oxygen species and nitric oxide acting through the coronary endothelium to promote pathological remodeling and increase myocardial stiffness.
This provides an appropriate transition into the third month, where the attention will turn to the myocardium and an analysis of cellular and molecular factors contributing to the development of HFpEF. Indeed, two prominent clinical features of HFpEF are diastolic dysfunction and myocardial hypertrophy. Drs. Ken Campbell and Vincent Sorrell (3) summarize changes to the cardiomyocyte, such as calcium handling and altered sarcomeric protein expression, that may cause diastolic dysfunction associated with HFpEF and discuss how these mechanisms may be manipulated to improve left ventricular function in these patients. Our final review comes from a team led by Drs. Frank Heinzel and Frank Edelmann (8), who explore the mechanisms driving myocardial structural abnormalities associated with HFpEF. This analysis focuses on left ventricular hypertrophy and associated structural changes presented in a diagnostic and therapeutic context and examines the impact of exercise on the remodeling process.

Ultimately, the goal of this collection is to stimulate new conversations and questions in an effort to improve understanding and treatment of a disease that has proven difficult to treat clinically. Is the best approach to treat the myocardium as has been traditionally done? What about the coronary vasculature or peripheral mechanisms? Is a combination of all these systemic avenues necessary? Finally, is the integrated effect of exercise on the entire cardiovascular system our best therapeutic option given the vast amount of clinical comorbidities that accompany HFpEF? We hope this *Journal of Applied Physiology* Highlighted Topic provides a basis for the scientific community to move forward in designing novel therapeutic options to effectively treat these patients.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

K.S.M. and C.A.E. drafted manuscript; K.S.M. and C.A.E. edited and revised manuscript; K.S.M. and C.A.E. approved final version of manuscript.

**REFERENCES**