Rationale and Study Design of Differences in Cardiopulmonary Exercise Capacity According to Coronary Microvascular Dysfunction and Body Composition in Patients with Suspected Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Coronary microvascular dysfunction (CMD) is one of the mechanisms of myocardial ischemia and left ventricular (LV) diastolic dysfunction, which is closely related to heart failure with preserved ejection fraction (HFpEF). Frailty, associated with sarcopenia, is often accompanied by HFpEF. In the present study, we aim to evaluate the relationship between CMD, body composition, and cardiopulmonary exercise capacity in patients with suspected HFpEF. We will enroll patients experiencing chest symptoms (chest pain or dyspnea) with an indication of non-obstructive coronary artery disease (<50% stenosis) on coronary angiography and preserved LV ejection fraction (≥50%) on echocardiography. All patients will undergo body composition analysis and adenosine stress echocardiography with the evaluation of coronary artery blood flow and maximal oxygen consumption by cardiopulmonary exercise test. LV end-diastolic pressure will be assessed using coronary angiography. Coronary flow reserve (CFR) is defined as the ratio of the peak to the baseline mean diastolic velocity of coronary blood flow. A CFR <2.3 is defined as coronary microvascular dysfunction. The correlation of CFR, and body composition with LV diastolic function and cardiopulmonary exercise capacity will be assessed. This trial will suggest the specific phenotypes of HFpEF according to body composition and CMD and the specific management of the different phenotypes of HFpEF.

Trial Registration: ClinicalTrials.gov Identifier: NCT04822649

Keywords: Exercise tolerance; Frailty; Heart failure; Sarcopenia
INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) has become the dominant form of heart failure as society becomes aging.\(^1\) HFpEF consists of heterogeneous phenotypes. Coronary microvascular dysfunction (CMD) is often accompanied by HFpEF. In recent studies, approximately 70% of patients with HFpEF had CMD.\(^2\)\(^3\) Previous studies have shown that CMD is associated with poor exercise capacity and adverse outcomes.\(^4\) Frailty, which is defined as an exaggerated decline in function and reserve of multiple physiological systems, is common in HFpEF as patients with HFpEF are typically elderly and have several co-morbidities.\(^5\)

Sarcopenia is a major component of the pathophysiology of frailty and plays an important role in the development of HFpEF.\(^6\) It is important to understand the connections between CMD, frailty, and exercise capacity in patients with HFpEF in order to classify patients with HFpEF into specific phenotypes and find the appropriate management for each patient. In the present study, we will evaluate the relationship between cardiopulmonary exercise capacity of patients with suspected HFpEF and CMD or frailty by measuring coronary flow reserve (CFR), body composition, and maximal oxygen consumption (\(\text{VO}_2\text{max}\)).

STUDY DESIGN

This study is a single-center, cross-sectional study conducted at the Korea University Anam Hospital, Seoul, Republic of Korea. The study protocol was reviewed and approved by the Institutional Review Board of Korea University Anam Hospital (IRB number: 2020AN0030). Informed consent has been obtained from all enrolled patients.

Trial population

Adult patients experiencing chest discomfort symptoms with an indication of non-obstructive coronary artery disease (<50% stenosis) on coronary angiography (CAG) and preserved ejection fraction (≥50%) on echocardiography will be eligible for the study. Patients with clinically significant (≥moderate) valvular heart disease, chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m\(^2\)), and chronic obstructive pulmonary disease will be excluded. Specific criteria for inclusion and exclusion are shown in Tables 1 and 2, respectively.

| Table 1. Inclusion criteria |
|-----------------------------|
| Criteria                    |
| Age 20 to 80 years          |
| Typical/atypical chest pain or dyspnea |
| Non-obstructive coronary artery (≤50% stenosis) on coronary angiography |

| Table 2. Exclusion Criteria |
|-----------------------------|
| Criteria                    |
| Clinically significant (≥moderate) valvular heart disease and congenital heart disease |
| Chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m\(^2\)) or end-stage renal failure undergoing hemodialysis or peritoneal dialysis |
| Asthma, chronic obstructive pulmonary disease and primary pulmonary hypertension |
| Receiving anticancer drugs |
| Vasculitis associated with autoimmune diseases |
| Difficulty in performing exercise load evaluation (treadmill, bicycle ergometer) |
| Atrial fibrillation |
| Atrophic ventricular block with more than second degrees, symptomatic bradycardia, cryo-node failure syndrome, Wolff-Parkinson-White (WPW) patients |
Study flow
Patients who meet the criteria for selection and exclusion will be screened, and informed consent will be obtained on the same day of CAG. After performing the body composition analysis, adenosine echocardiography will be performed with the evaluation of coronary blood flow by Doppler echocardiography. VO₂max by cardiopulmonary exercise test (CPET) will be performed within 2 weeks from the day of CAG.

CAG and measurement of left ventricular (LV) end-diastolic pressure
Conventional CAG will be performed using standard techniques. With a trans-radial or transfemoral approach, 4 or 5 Fr coronary catheters are used to engage the coronary artery ostium. Optimal coronary injection with radiopaque contrast agents will ensure complete opacification of the major coronary arteries and side branches. Angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening. After performing CAG, LV end-diastolic pressure will be measured with a 5 Fr pigtailed catheter. To assess the concomitant microvascular or epicardial coronary artery spasm, the spasm provocation test will be performed using intracoronary ergonovine.

Body composition analysis
Using a body composition analyzer (InBody S10; InBody, Cerritos, CA, USA), impedance is measured in six frequency bands (1, 5, 50, 250, 500, and 1,000 kHz) for each of the 5 parts (right arm, left arm, torso, right leg, left leg). Reactance is measured in three frequency bands (5, 50, 250 kHz for each of the 5 parts (right arm, left arm, torso, right leg, left leg). Skeletal muscle mass, body fat mass, visceral fat area, subcutaneous fat area, total body water, and intracellular and extracellular water will be also assessed.

CFR and echocardiography
Transthoracic echocardiographic studies will be performed using a commercially available ultrasound machine (Vivid E95; GE Healthcare, Liestal, Switzerland).

The color Doppler flow of the distal left anterior descending artery will be examined from the modified apical four-chamber view in the anterior interventricular groove (Figure 1A). Pulsed wave Doppler registered blood flow velocity patterns using a sample volume (2–3.0 mm) placed on the color signal (Figure 1B). The ultrasound beam will be aligned parallel to the vessel flow as much as possible. The velocity scale of color Doppler was set to 0.21 m/s. Adenosine will be administered at 140 µg/kg/min. Coronary flow Doppler images will be acquired before and after adenosine infusion in the same part of the artery. Arterial pressure, heart rate, oxygen saturation, and electrocardiogram will be monitored during the test. Comprehensive echocardiographic assessment including parameters related to LV diastolic function (e.g., early diastolic mitral inflow velocity [E], early diastolic mitral annular velocity [e’], left atrial volume index, tricuspid regurgitation peak velocity), LV systolic function (e.g., LV ejection fraction, global longitudinal strain, circumferential strain, radial strain, LV twist and untwisting rate, and myocardial work), and right ventricular function (e.g., tricuspid annular peak systolic velocity) will be performed at rest and peak stress. The mean diastolic coronary flow velocity will be measured. CFR is defined as the peak-to-baseline mean diastolic velocity of the coronary flow. CMD is typically defined as impaired vasodilation of arterioles and CFR less than 2.3.
Cardiopulmonary exercise capacity

Maximal tolerable treadmill exercise test with modified Bruce protocol or bicycle ergometer for patients with orthopedic problems will be used to measure VO\textsubscript{2} max and % predicted VO\textsubscript{2} max with exhalation gas analysis (Quark CPET; COSMED, Rome, Italy). After calibrating the gas and flowmeter, patients will put on a leak-free sealing mask. Other measurements during CPET include total exercise time, metabolic equivalents at the ventilatory anaerobic threshold, and respiratory exchange ratio.

Endpoints

The primary endpoint of the study is the correlation of cardiopulmonary exercise capacity between CMD and body composition in patients with suspected HFpEF. According to CMD and body composition, the enrolled patients can be divided into specific phenotypes. The secondary endpoint is the correlation of CMD and body composition with echocardiographic parameters.

Statistical analysis

Continuous variables will be described as means and standard deviations. Categorical data will be expressed as percentages. Comparisons of proportions will be performed using the Pearson $\chi^2$ test and Fisher’s exact test. Differences between the baseline characteristics according to the presence of CMD or different body compositions will be compared using an independent sample t-test or analysis of variance. The correlation between CMD or body composition and cardiopulmonary exercise capacity will be evaluated using correlation analysis. The p value $<0.05$ will be considered statistically significant.

DISCUSSION

Patients with chest symptoms showed poor outcomes and quality of life, even without obstructive coronary artery disease, compared to patients without chest symptoms.\textsuperscript{13} This is mainly due to the heterogeneity of the population, which precludes physicians from appropriate management for them. HFpEF is a significant part of this population and has various pathophysiological characteristics (Figure 2). CMD is known to be closely related to HFpEF and is associated with poor prognosis, worsening diastolic function, and increased
rates of adverse cardiovascular events such as sudden cardiac death, myocardial infarction, congestive heart failure, and coronary revascularization.\textsuperscript{5,4-15}

It is known that CMD is associated with poor exercise capacity. In a previous study of women experiencing chest pain without overt coronary artery disease, patients with CMD showed markedly reduced exercise capacity compared with sex-matched controls.\textsuperscript{4} With greater stiffness of the smaller LV, women are more vulnerable to ischemic insults from CMD.\textsuperscript{16} Poor exercise capacity can be partially explained by the results of a recent study of simultaneous evaluation of coronary pressure and flow velocity during rest, supine bicycle exercise, and adenosine-mediated hyperemia. In this study, patients with CMD showed myocardial ischemia and abnormal coronary perfusion during exercise.\textsuperscript{17}

Frailty is also related to Hfpef and sarcopenia is a major component of the pathophysiology of frailty.\textsuperscript{7} Aging and a sedentary lifestyle decreases muscle mass and daily energy expenditure as well as increases fat mass.\textsuperscript{18} Sarcopenia can contribute to the development of Hfpef through various metabolic and endocrine abnormalities including inflammation, insulin resistance, myokine dysregulation, amino acid deficiency, and adiponectin dysregulation.\textsuperscript{18} Different body compositions affect the clinical outcome of patients with heart failure. In patients with heart failure, reduced axial skeletal muscle, but not fat, was closely related to mortality.\textsuperscript{19} Sarcopenia was also strongly linked to low cardiopulmonary capacity and quality of life in patients with Hfpef.\textsuperscript{20} In patients with heart failure with reduced ejection fraction, patients with low lean body fat mass showed a lower survival rate than patients with high body fat mass.\textsuperscript{21}
It is difficult to determine the appropriate management for HFpEF because HFpEF consists of various pathophysiological features. It is essential to differentiate and target specific phenotypes from the heterogeneous pool in order to find the most effective management. In the present study, we will evaluate the prevalence of CMD and characteristics of body composition in patients with suspected HFpEF and their correlation with exercise capacity according to the presence of CMD and sarcopenia. Furthermore, we anticipate that finding the specific phenotypes of HFpEF will provide directions for the best treatment strategy for HFpEF.

REFERENCES

1. Bronzwaer JG, Paulus WJ. Diastolic and systolic heart failure: different stages or distinct phenotypes of the heart failure syndrome? Curr Heart Fail Rep 2009;6:281-6. 
PUBMED | CROSSREF

2. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018;39:3439-50. 
PUBMED | CROSSREF

3. Yang JH, Obokata M, Reddy YNV, Redfield MM, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. Eur J Heart Fail 2020;22:432-41. 
PUBMED | CROSSREF

4. Bechsgaard DF, Hove JD, Suhrs HE, et al. Women with coronary microvascular dysfunction and no obstructive coronary artery disease have reduced exercise capacity. Int J Cardiol 2019;293:1-9. 
PUBMED | CROSSREF

5. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISe (Women’s Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825-32. 
PUBMED | CROSSREF

6. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms, prevalence, prognosis, assessment, and management. JACC Heart Fail 2019;7:1001-11. 
PUBMED | CROSSREF

7. Kinugasa Y, Yamamoto K. The challenge of frailty and sarcopenia in heart failure with preserved ejection fraction. Heart 2017;103:184-9. 
PUBMED | CROSSREF

8. Généreux P, Mehran R, Leon MB, Bettinger N, Stone GW. Classification for assessing the quality of diagnostic coronary angiography. J Invasive Cardiol 2017;29:417-20. 
PUBMED | CROSSREF

9. Leopold JA, Faxon DP. Diagnostic cardiac catheterization and coronary angiography. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. editors. Harrison’s Principles of Internal Medicine. 20th ed. New York: McGraw-Hill Education; 2018.

10. Kim SM, Shim WJ, Lim HE, et al. Assessment of coronary flow reserve with transthoracic Doppler echocardiography: comparison with intracoronary Doppler method. J Korean Med Sci 2000;15:139-45. 
PUBMED | CROSSREF

11. Zagatina A, Zhuravskaya N. The additive prognostic value of coronary flow velocity reserve during exercise echocardiography. Eur Heart J Cardiovasc Imaging 2017;18:1179-84. 
PUBMED | CROSSREF

12. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation (WISE) study: part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol 2006;47:84-20. 
PUBMED | CROSSREF

13. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women’s Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J 2006;27:1408-15. 
PUBMED | CROSSREF

14. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J 2018;39:840-9. 
PUBMED | CROSSREF
15. Park SM, Wei J, Cook-Wiens G, et al. Left ventricular concentric remodelling and functional impairment in women with ischaemia with no obstructive coronary artery disease and intermediate coronary flow reserve: a report from the WISE-CVD study. Eur Heart J Cardiovasc Imaging 2019;20:875-82.

16. Regitz-Zagrosek V. Sex and gender differences in heart failure. Int J Heart Fail 2020;2:157-81.

17. Rahman H, Ryan M, Lumley M, et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. Circulation 2019;140:1805-16.

18. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr 2014;33:737-48.

19. Selvaraj S, Kim J, Ansari BA, et al. Body composition, natriuretic peptides, and adverse outcomes in heart failure with preserved and reduced ejection fraction. JACC Cardiovasc Imaging 2021;14:203-15.

20. Bekfani T, Pellicori P, Morris DA, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: impact on muscle strength, exercise capacity and quality of life. Int J Cardiol 2016;222:41-6.

21. Thomas E, Gupta PP, Fonarow GC. Bioelectrical impedance analysis of body composition and survival in patients with heart failure. Clin Cardiol 2019;42:129-35.