Int J Heart Fail. 2021 Oct;3(4):237-243
https://doi.org/10.36628/ijhf.2021.0029
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure IJHF

Trial Design

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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Received: Jul 4, 2021
Revised: Aug 20, 2021
Accepted: Sep 9, 2021

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Trial Registration
ClinicalTrials.gov Identifier: NCT04822649

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

Funding
This study is funded by the KSE Sanhak Grant and Ildong Pharmaceutical Co.

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kim MN, Park SM; Data curation: Park SM; Funding acquisition: Park SM; Investigation: Kim SR, Cho DH, Kim MN, Park SM; Methodology: Kim SR, Cho DH, Kim MN, Park SM; Supervision: Park SM; Validation: Kim SR, Cho DH, Kim MN, Park SM; Visualization: Kim SR; Writing - original draft: Kim SR; Writing - review & editing: Kim SR, Park SM.

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][5] 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.[6] Sarcopenia is a major component of the pathophysiology of frailty and plays an important role in the development of HFpEF.[7] 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 (VO_2max).

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
Preserved ejection fraction (≥50%) on echocardiography

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/1.73m^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
Atrioventricular 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. VO_2max 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.[8] Angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.[9] 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**).[10] 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.[11] 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′], E/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.[12]

https://doi.org/10.36628/ijhf.2021.0029

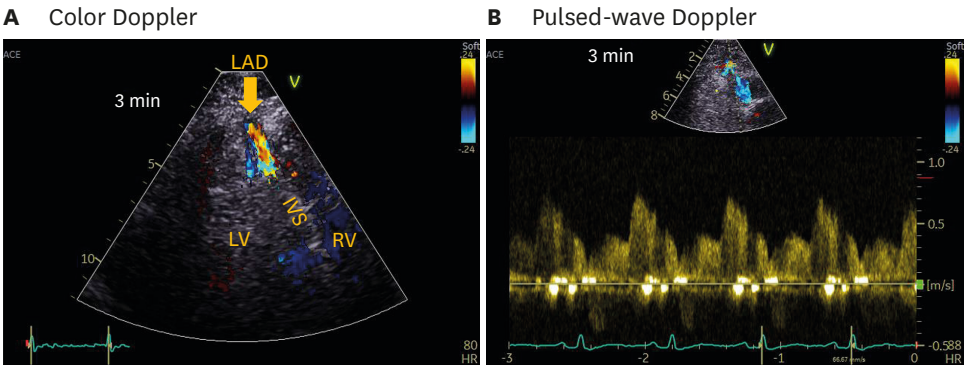

Figure 1. Coronary blood flow by transthoracic echocardiography.
(A) Transthoracic color Doppler echocardiography shows blood flow in the distal LAD from the modified apical four-chamber view in the anterior interventricular groove (yellow arrow). (B) Pulsed-wave Doppler flow in the distal LAD shows a characteristic biphasic coronary flow pattern, consisting of systolic and diastolic phases with higher velocity during diastole.
IVS = interventricular septum; LAD = left anterior descending artery; LV = left ventricle; RV = right ventricle.

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_2 max and % predicted VO_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 χ^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.[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

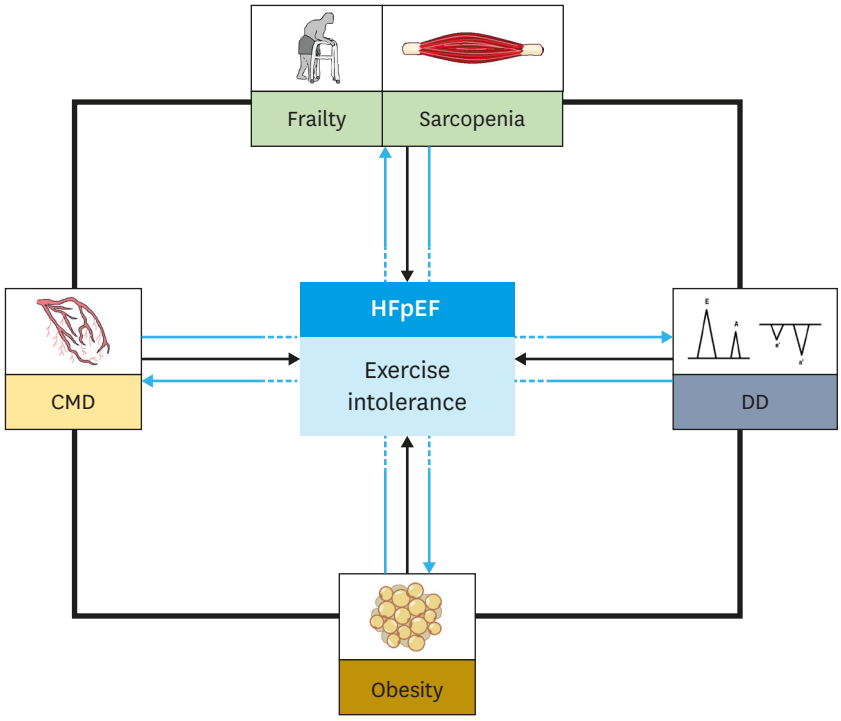

Figure 2. Relationship between CMD, frailty, obesity, DD, and HFpEF with exercise intolerance. Each component is closely related to each other and can be presented as HFpEF with decreased exercise capacity.
CMD = coronary microvascular dysfunction; DD = diastolic dysfunction; HFpEF = heart failure with preserved ejection fraction.

rates of adverse cardiovascular events such as sudden cardiac death, myocardial infarction, congestive heart failure, and coronary revascularization.[5)14)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.[4)] With greater stiffness of the smaller LV, women are more vulnerable to ischemic insults from CMD.[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.[17)]

Frailty is also related to HFpEF and sarcopenia is a major component of the pathophysiology of frailty.[7)] Aging and a sedentary lifestyle decreases muscle mass and daily energy expenditure as well as increases fat mass.[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.[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.[19)] Sarcopenia was also strongly linked to low cardiopulmonary capacity and quality of life in patients with HFpEF.[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.[21)]

https://doi.org/10.36628/ijhf.2021.0029

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.

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