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Effects of sarcopenia, body mass indices, and sarcopenic obesity on diastolic function and exercise capacity in Koreans

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ABSTRACT

Aims: Obesity induces left ventricular diastolic dysfunction and ultimately causes heart failure. Sarcopenic obesity is common in heart failure with preserved ejection fraction (HFpEF). However, the precise mechanism by which sarcopenic obesity is related to HFpEF is poorly understood. We aimed to evaluate the combined effect of sarcopenia (SP) and obesity on left ventricular diastolic function and exercise capacity.

Methods: This study included 733 healthy subjects who underwent health check-ups in a tertiary hospital in Korea. All participants were categorized into four groups: non-SP/non-obese, SP/non-obese, non-SP/obese, and SP/obese. Comprehensive echocardiography with cardiopulmonary exercise testing was performed. Diastolic dysfunction was defined as an E/e' ratio ≥ 10.

Results: Across SP and obesity groups, a gradual decrease in e' velocity and an increase in the E/e' ratio was noted after adjustment for age and sex. Furthermore, a gradual decrease in percent-predicted peak VO_2 was observed across the groups. In the multivariate logistic regression analysis, the SP/obese group had the highest risk for diastolic dysfunction (OR 4.27, 95% CI 2.41–7.57), followed by the non-SP/obese group (OR 2.88, 95% CI 1.57–5.29) and the SP/non-obese group (OR 1.90, 95% CI 1.01–3.56) compared with the reference (non-SP/non-obese) group even after controlling for various confounders.

Conclusion: Sarcopenic obesity was associated with impaired diastolic function and decreased exercise capacity, suggesting a possible mechanism by which sarcopenic obesity contributes to the development of HFpEF.

1. Introduction

Obesity induces left ventricular (LV) diastolic dysfunction and ultimately causes heart failure, particularly heart failure with preserved ejection fraction (HFpEF) [1,2]. HFpEF is an important health issue that adversely affects morbidity and mortality similarly to heart failure with reduced ejection fraction [3,4]. Sarcopenic obesity, a condition characterized by excess body fat combined with decreased muscle mass, is a common phenotype in HFpEF [5,6]. However, the precise mechanism by which sarcopenic obesity is related to HFpEF is poorly understood. Previous studies have separately explored the roles of sarcopenia and obesity in the pathogenesis of HFpEF [7–12], although these two conditions often coexist. It is clinically relevant to determine how both sarcopenia and obesity affect LV function to characterize the progression from a subclinical stage to clinical overt heart failure, given that these two conditions are modifiable.

Inappropriately elevated LV filling pressure, even at a low grade of exercise, is a key finding of HFpEF [13], and in this regard, the E/e' ratio along with other diastolic parameters is a simple, clinically useful marker for identifying the preclinical/clinical stage of HFpEF, although such parameters have some limitations [10,14–16]. Furthermore, higher E/e' ratio is associated with decreased exercise capacity, expressed as depressed peak VO_2 [17,18]. We hypothesized that sarcopenic obesity is associated with impaired diastolic function and exercise intolerance compared with other phenotypes. The primary aim of this study was to identify the combined effect of sarcopenic obesity on heart structure and function, especially focusing on LV diastolic function. Furthermore,

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BIA, bioelectrical impedance analysis; BMI, body mass index; BP, blood pressure; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HOMA-IR, homeostatic model assessment-estimated insulin resistance; LV, left ventricular; OR, odds ratio.

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we aimed to confirm whether these different obesity-sarcopenia phenotypes were related to exercise capacity using a cardiopulmonary exercise test.

2. Methods

2.1. Study population

We retrospectively reviewed the medical records of 1438 healthy individuals who underwent a cardiopulmonary exercise test as part of a comprehensive health examination in a tertiary hospital in Korea between January 2009 and April 2017. To evaluate the independent effect of sarcopenic obesity on LV function and exercise capacity, we excluded patients according to the following criteria, which could possibly affect the results: 1) aged <20 or ≥80 years, 2) known cardiovascular diseases including atrial fibrillation, 3) diagnosed with hypertension (blood pressure [BP] ≥ 140/90 mmHg or on hypertension medication) and/or diabetes (fasting glucose ≥126 mg/dL or on diabetes medication), 4) hemoglobin <10 mg/dL, 5) significant lung disease confirmed by chest X-ray or a pulmonary function test, 6) asymptomatic but significant structural heart disease confirmed by echocardiography, 7) early termination of the exercise test due to other reasons, and 8) non-Korean descent. We also excluded those with missing echocardiography and/or body composition analysis data. Finally, 733 subjects were entered into the analysis. The institutional ethics committee of Seoul St. Mary's Hospital approved the study protocol (KC18RESI0137). Informed consent was waived due to the retrospective design.

All participants were instructed to fast overnight for at least 12 h, to avoid excessive exercise, and to refrain from drinking alcohol or caffeine. The detailed process of health check-ups in our hospital is provided elsewhere [18,19]. In brief, we acquired data on demographics, health-related behaviors, previous medical history, and medication use by questionnaires and interviews. Anthropometric measurements were made by trained staff while patients wore light clothing and were barefoot. Body mass index (BMI) was calculated as body weight/squared height (kg/m^2), and individuals with a BMI of 25 kg/m^2 or greater were defined as obese based on the obesity criteria for the Korean population [20]. BP was measured in a quiet room after resting for at least 10 min using an automated BP device (TM-2665P, A&D, Tokyo, Japan). BP was checked at least twice over a 2-min interval, and the average value was taken. After at least 5 min of rest, heart rate was measured by palpating the radial pulse for 15 s and was then multiplied by 4. Blood samples were collected via the antecubital vein. Lipid profiles and blood glucose were measured by the enzymatic method. Insulin levels were determined using a radioimmunoassay kit. Homeostatic model assessment-estimated insulin resistance (HOMA-IR), a measure of insulin resistance, was assessed using the online HOMA2 calculator.

2.2. Body composition data: definition of sarcopenia

Body composition was evaluated using a bioelectrical impedance analysis (BIA) device (InBody 720, Biospace, Seoul, Korea). The subjects were instructed to step on the foot electrodes while barefoot and grasp the hand electrode cables. The build-in software calculator displays the fat percent (fat mass indexed to body weight, %) and the muscle percent (muscle mass indexed to body weight, %) within a few minutes. Based on the study by Janssen et al., subjects were considered normal if their muscle percent was greater than −1 standard deviation above the sex-specific mean for young adults (aged 18–39); subjects who did not meet the definition of normal muscle percent were considered to have sarcopenia [21]. In this study, the muscle percent (mean ± standard deviation) was 43.8 ± 3.4% for young males and 37.7 ± 0.6% for young females. Therefore, sarcopenia was defined as a muscle percent <40.4% for males or <37.1% for females.

2.3. Echocardiographic data: assessment of LV structure and function

All echocardiographic data were obtained using a GE Vivid 7 Ultrasound system by a trained sonographer (Registered Diagnostic Cardiac Sonographer) according to the reported guidelines [22]. The LV wall thickness was measured from the parasternal long-axis view in M-mode. LV mass was obtained by the linear method and indexed to body surface area. LV systolic function was expressed as LV ejection fraction derived from the biplane Simpson method. LV diastolic function was determined through pulse-wave Doppler of mitral inflow (E wave velocity, A wave velocity) and tissue Doppler imaging of the septal annulus (e' velocity, a' velocity). The E/e' ratio, which represents the LV filling pressure, was also calculated. The left atrial volume index, which reflects the cumulative effect of LV filling pressure over time, was acquired from the biplane Simpson method and indexed to body surface area [23]. Diastolic dysfunction was defined as an E/e' ratio ≥ 10.

2.4. Cardiopulmonary exercise data

To evaluate exercise capacity, a symptom-limited treadmill test was performed under supervision of a trained physiologist according to the modified Bruce protocol with simultaneous respiratory gas analysis (Schiller, Baar, Switzerland). All of the participants reached ≥85% of their age-predicted maximal heart rate (220–age) during the examination. Peak oxygen consumption was measured and recorded in two forms: 1) peak VO_2, the most common parameter used to indicate exercise capacity, which accounts for an individual's body weight (ml/kg/min) and 2) percent-predicted peak VO_2 (%) derived from the Wasserman equation [24]. We mainly adopted the results from percent-predicted peak VO_2 because the percent-predicted peak VO_2 showed a clearer group difference than the absolute peak VO_2 value in our study and accounted for age- and sex-varying effects [24,25]. We defined exercise intolerance as a percent-predicted peak VO_2 <80%. The cut-off value for exercise intolerance (among relatively healthy subjects) was chosen considering that a percent-predicted peak VO_2 ≥80% is generally regarded as low risk for heart failure [26]. Ventilatory efficiency was expressed as the VE/VCO_2 slope [24].

2.5. Statistical analysis

To determine the effect of different sarcopenia/obesity categories on LV structure and function and on exercise intolerance, the entire study population was divided into 4 groups: non-sarcopenia/non-obese, sarcopenia/non-obese, non-sarcopenia/obese, and sarcopenia/obese. We compared the clinical, laboratory, body composition, cardiopulmonary exercise, and echocardiographic data across the different groups using analysis of variance (ANOVA), chi-square test, or Fisher's exact test. The results are presented as the mean ± standard deviation or the number and percentage, as indicated. To identify age- and sex-independent effects of the sarcopenia/obesity phenotype on LV structure and function, which was the main outcome of the present study, we further performed an analysis of covariance (ANCOVA), and the data are presented as the adjusted mean ± standard error. Comparisons between groups were performed using the Bonferroni post hoc test. Relationships between diastolic parameters and body measurements (BMI or muscle percent) were analyzed using Pearson's correlation and multivariate linear regression analysis. Finally, multivariate logistic regression analysis (stepwise method) was performed to determine the risk for diastolic dysfunction according to the different sarcopenia/obese categories after controlling for possible confounding factors. To avoid collinearity, variables were carefully selected. Data were presented as odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using SPSS version 21.0 software (IBM, Armonk, NY, USA). All statistics were two-sided, and $p < 0.05$ was considered significant.

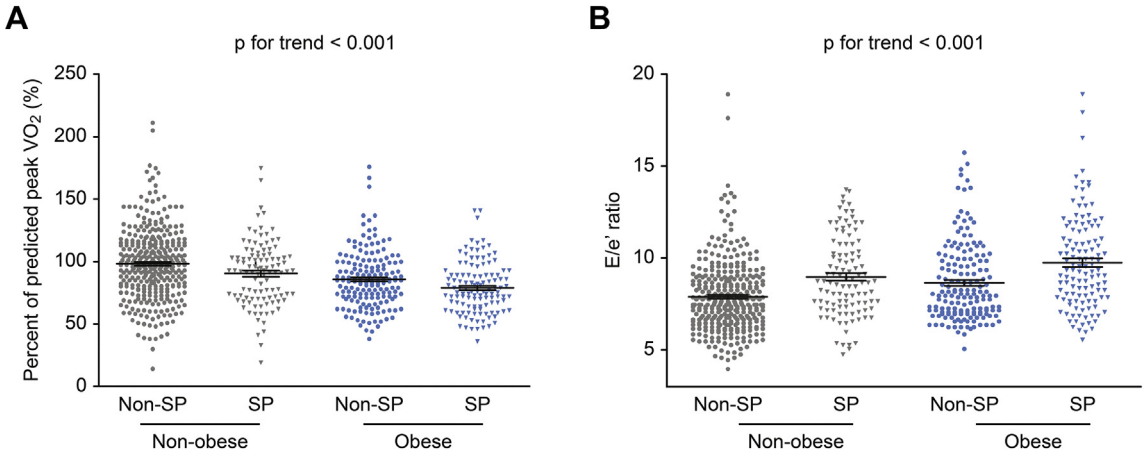

Fig. 1. Differences in exercise capacity and diastolic function according to sarcopenia/obesity category. Note the gradual decrease in percent-predicted peak VO_2 (A) and worsening diastolic function (B) according to sarcopenia/obesity group. The presence of obesity is presented as color (grey for the non-obese group, blue for the obese group), and the presence of sarcopenia is presented as shape (inverted triangle for those with sarcopenia, circle for non-sarcopenia). SP; sarcopenia. P for trend was determined by ANOVA.

3. Results

3.1. Baseline characteristics: demographic and exercise capacity findings

A total of 733 participants (mean age, 52.6 ± 8.8 years; 58.3% male) were included in this study. The mean BMI was 23.8 ± 3.0 kg/m^2 (non-obese group, 22.0 ± 1.8 kg/m^2; obese group was 26.8 ± 2.0 kg/m^2), and the mean muscle percent was 40.4 ± 2.8% (non-sarcopenia group, 42.4 ± 2.8%; sarcopenia group, 35.9 ± 2.8%). Significant differences in age and sex were demonstrated across the 4 groups; individuals with sarcopenia/obesity were slightly older and were more frequently female. Insulin resistance, assessed by HOMA-IR, exhibited a gradual increase with sarcopenia/obesity. Exercise capacity, expressed as percent-predicted peak VO_2, was gradually decreased across the sarcopenia/obesity groups (Fig. 1-A and Table 1). The prevalence of exercise intolerance also gradually increased across groups. The characteristics of the participants based on sarcopenia/obesity group are shown in Table 1.

3.2. Effect of sarcopenia/obesity on cardiac structure and function

There were significant group differences in LV wall thickness, LV mass index, and diastolic parameters across the 4 groups (Table 2). Individuals with sarcopenia/obesity had increased wall thickness and worse diastolic profile (increased A wave velocity, decreased e' velocity, and increased E/e' ratio, Fig. 1-B). This difference persisted after adjustment for age and sex (E/e' ratio: 8.3 ± 0.2 for non-sarcopenia/non-obese, 8.7 ± 0.2 for sarcopenia/non-obese, 9.2 ± 0.6 for non-sarcopenia/obese, and 10.1 ± 0.3 for sarcopenia/obese groups, presented as the adjusted mean ± standard error with an adjusted overall $p < 0.001$). However, LV systolic function, assessed by LV ejection fraction, did not exhibit statistically significant differences across the groups after adjustment for age and sex. The detailed echocardiographic data are provided in Table 2.

The E/e' ratio exhibited a positive correlation with BMI and a negative correlation with muscle percent. In general, the slope of the association between body measurements and E/e' was steeper for females

Table 1
Study population characteristics (n = 733).

	Non-SP/non-obese (n = 341)	SP/non-obese (n = 106)	Non-SP/obese (n = 166)	SP/obese (n = 120)	p value
Clinical variable					
Age, years	51.3 ± 9.0	55.7 ± 8.3	51.6 ± 7.7	54.9 ± 8.9	<0.001
Sex (male), n (%)	196 (57.5)	12 (11.3)	156 (94.0)	63 (52.5)	<0.001
Systolic BP, mmHg	117.4 ± 10.8	117.2 ± 10.8	121.0 ± 8.9	123.5 ± 9.0	<0.001
Heart rate, bpm	80.3 ± 11.5	78.1 ± 11.8	76.0 ± 11.3	79.0 ± 12.7	0.001
Body mass index, kg/m^2	21.8 ± 1.9	22.5 ± 1.3	26.3 ± 1.3	27.4 ± 2.6	<0.001
Body composition data					
Fat percent, %	23.0 ± 4.8	33.5 ± 2.9	24.8 ± 2.9	34.5 ± 4.9	<0.001
Muscle percent, %	42.5 ± 3.2	35.7 ± 1.9	42.4 ± 1.8	35.8 ± 4.6	<0.001
Laboratory findings					
HDL cholesterol, mg/dL	53.6 ± 13.1	53.9 ± 12.2	44.5 ± 10.2	48.0 ± 12.9	<0.001
HOMA-IR	1.42 ± 1.47	1.48 ± 1.25	2.33 ± 1.90	3.12 ± 3.17	<0.001
Cardiopulmonary exercise test findings					
Peak VO_2, ml/kg/min	26.0 ± 7.6	21.6 ± 6.9	28.4 ± 6.8	23.9 ± 6.1	<0.001
Percent-predicted peak VO_2, %	98.2 ± 28.3	90.5 ± 25.8	85.7 ± 23.0	78.9 ± 20.6	<0.001
VE/CO_2 slope	21.5 ± 5.0	23.3 ± 3.3	21.5 ± 3.9	22.2 ± 4.2	0.002
Exercise intolerance, n (%)[a]	81 (23.8)	41 (38.7)	71 (42.8)	68 (56.7)	<0.001

BP, blood pressure; HDL, high density lipoprotein; SP, sarcopenia.
[a] Exercise intolerance was defined as <80% of percent-predicted peak VO_2. Data are expressed as the mean ± standard deviation or numbers with percentages. p values are for ANOVA.

Table 2
Structure and function of left ventricle according to SP/obesity category.

	Unadjusted mean ± standard deviation					Age-, sex- adjusted mean ± standard error				
	Non-SP/non-obese (n = 341)	SP/non-obese (n = 106)	Non-SP/obese (n = 166)	SP/obese (n = 120)	p value	Non-SP/non-obese (n = 341)	SP/non-obese (n = 106)	Non-SP/obese (n = 166)	SP/obese (n = 120)	p value
IVSd, mm	8.0 ± 1.1	7.8 ± 1.2	8.8 ± 1.0*†	8.7 ± 1.0*†	<0.001	8.1 ± 0.1	8.1 ± 0.1	8.5 ± 0.1*†	8.7 ± 0.1*†	<0.001
PWd, mm	8.2 ± 1.0	8.0 ± 1.2	8.8 ± 1.1*†	8.7 ± 1.1*†	<0.001	8.2 ± 0.1	8.3 ± 0.1	8.6 ± 0.1*	8.7 ± 0.1*†	<0.001
LV mass index, g/m^2	76.1 ± 14.7	76.4 ± 15.1	84.8 ± 17.7*†	81.9 ± 15.3*†	<0.001	76.8 ± 0.8	77.8 ± 1.6	83.1 ± 1.2*	81.1 ± 1.4*	<0.001
LVEF, %	67.0 ± 4.9	68.2 ± 5.6	65.6 ± 7.1†	67.2 ± 5.0	0.003	67.0 ± 0.3	67.8 ± 0.6	66.0 ± 0.5	67.2 ± 0.5	0.135
LAVI, ml/m^2	21.4 ± 7.0	20.9 ± 8.1	22.5 ± 8.3	22.9 ± 6.6	0.094	21.6 ± 0.4	19.9 ± 0.8	23.1 ± 0.6†	22.5 ± 0.7	0.011
E velocity, cm/s	64.0 ± 13.5	65.0 ± 13.2	60.9 ± 12.5	62.5 ± 14.0	0.041	63.5 ± 0.7	62.0 ± 1.3	63.7 ± 1.0	62.8 ± 1.1	0.751
A velocity, cm/s	60.2 ± 13.6	66.0 ± 12.1*	63.6 ± 13.4*	67.7 ± 13.2*	<0.001	61.2 ± 0.6	62.9 ± 1.2	64.9 ± 1.0*	65.9 ± 1.1*	<0.001
e' velocity, cm/s	8.5 ± 2.1	7.7 ± 2.3*	7.3 ± 1.9*	6.8 ± 1.9*†	<0.001	8.3 ± 0.1	7.9 ± 0.2	7.3 ± 0.1*	7.0 ± 0.2*†	<0.001
a' velocity, cm/s	8.9 ± 1.9	8.9 ± 1.5	9.3 ± 1.8	9.2 ± 1.6	0.065	9.0 ± 0.1	9.2 ± 0.2	9.0 ± 0.1	9.1 ± 0.2	0.645
E/e' ratio	7.8 ± 1.9	8.9 ± 2.1*	8.6 ± 2.1*	9.7 ± 2.6*†‡	<0.001	8.0 ± 0.1	8.3 ± 0.2	9.0 ± 0.2*	9.4 ± 0.2*†	<0.001

SP, sarcopenia; IVSd, interventricular septal thickness at diastole; PWd, posterior wall thickness at diastole, LVEF, left ventricular ejection fraction; LAVI, left atrial volume index.
* p < 0.05 versus non-SP/non-obese group.
† p < 0.05 versus SP/non-obese group.
‡ p < 0.05 versus non-SP/obese group.

than for males (Fig. 2-A, scatter plot for BMI and E/e', $r = 0.328$ for females, $r = 0.245$ for males; Fig. 2-B, scatter plot for muscle percent and E/e', $r = -0.345$ for females, $r = -0.261$ for males, all $p < 0.001$). Furthermore, we included another index, the fat mass/muscle mass ratio, and plotted the association between the E/e' ratio and fat mass/muscle mass ratio (Fig. 2-C). This index showed a positive correlation with the E/e' ratio. Interestingly, the distribution of fat mass/muscle mass was predominantly above 1 in females, but below 1 in males, reflecting a sex-specific predominance in body composition. After adjustment for age, sex, hemodynamic parameters, LV mass index, and laboratory findings, the E/e' ratio showed a positive association with BMI (adjusted β-coefficient 0.185, $p < 0.001$) and a negative association with muscle percent (adjusted β-coefficient −0.136, $p < 0.001$) (Table 3).

3.3. Risk of diastolic dysfunction according to sarcopenia/obesity

Individuals with obesity had a 3.0-fold (95% CI 1.9–4.8) greater risk for diastolic dysfunction than non-obese subjects regardless of confounding factors (Table 4). Subjects with sarcopenia had a 2.3-fold (95% CI 1.4–3.5) greater risk for diastolic dysfunction than their non-sarcopenic counterparts regardless of confounding factors (Table 4). We further evaluated the combined effect of sarcopenia and obesity on the risk of diastolic dysfunction and found that the risk gradually increased across the sarcopenia/obesity groups ($p < 0.001$). Compared with the non-sarcopenia/non-obese group (reference), the sarcopenia/obese group had the highest risk for diastolic dysfunction (adjusted OR 4.274, 95% CI 2.414–7.570), followed by the non-sarcopenia/obese group (adjusted OR 2.883, 95% CI 1.572–5.288) and the sarcopenia/non-obese group (adjusted OR 1.901, 95% CI 1.014–3.564), independent of age, sex, systolic BP, LV mass index, heart rate, level of high density lipoprotein cholesterol, and HOMA-IR (Fig. 3, supplementary Table A.1). Sex-specific data are provided in Table 5 and supplementary Table A.2. In general, females showed a stronger association between body measurements and LV diastolic dysfunction than males.

4. Discussion

We investigated the effect of sarcopenic obesity on LV diastolic function and its relationship to exercise intolerance in community-dwelling healthy Korean subjects who were free of cardiovascular diseases. The present study revealed that obesity, particularly sarcopenic obesity, had worse diastolic function and decreased exercise capacity compared with other phenotypes. The associations of body measurements (BMI and muscle percent) and LV diastolic function were steeper for females than for males. Both obesity and sarcopenia elevated the risk of diastolic dysfunction compared with their counterparts. The novel and key finding was that individuals with sarcopenic obesity had a greater risk for diastolic dysfunction than non-sarcopenic obese subjects, although obesity itself conferred an elevated risk for diastolic dysfunction. These results were independent of age, sex, systolic BP, heart rate, degree of LV hypertrophy, lipid profile, and insulin resistance. The present findings imply that maintaining muscle mass might be a helpful strategy to prevent the risk of diastolic dysfunction and, ultimately, HFpEF, even in obese subjects who are at high risk for developing HFpEF.

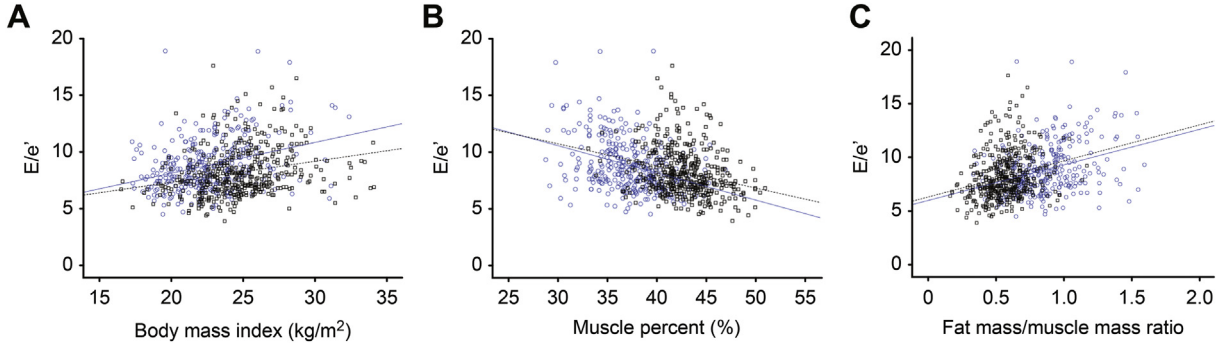

Fig. 2. Association between body measurements and E/e' ratio. A positive relationship between BMI and E/e' was noted (A). Conversely, an inverse relationship between muscle mass percent and E/e' was observed (B). Of note, females (blue circles with blue line) had a steeper slope of the association between body measurements and E/e' ratio than males (black square with black dotted line). The new index, the fat mass/muscle mass ratio, showed a positive correlation with E/e' (C). Interestingly, the distribution of the fat mass/muscle mass ratio was predominantly above 1 in females (blue circle with blue line) but below 1 in males (black square with black dotted line). The correlation, r, for fat mass/muscle mass ratio was 0.344 for females and 0.241 for males ($p < 0.001$).

Table 3
Multiple linear regression analysis of the association between body measurements and diastolic parameters.

	E' velocity		E/e' ratio	
	β-coefficient	p value	β-coefficient	p value
Body mass index, kg/m^2				
Unadjusted	−0.216	<0.001	0.157	<0.001
Adjusted[a]	−0.207	<0.001	0.205	<0.001
Adjusted[b]	−0.202	<0.001	0.185	0.001
Muscle percent, %				
Unadjusted	0.089	<0.001	−0.168	<0.001
Adjusted[a]	0.152	<0.001	−0.125	<0.001
Adjusted[b]	0.139	<0.001	−0.136	<0.001

[a] p value after adjustment for age and sex.
[b] p value after adjustment for age, sex, systolic blood pressure, heart rate, left ventricular mass index, high density lipoprotein cholesterol, and HOMA-IR.

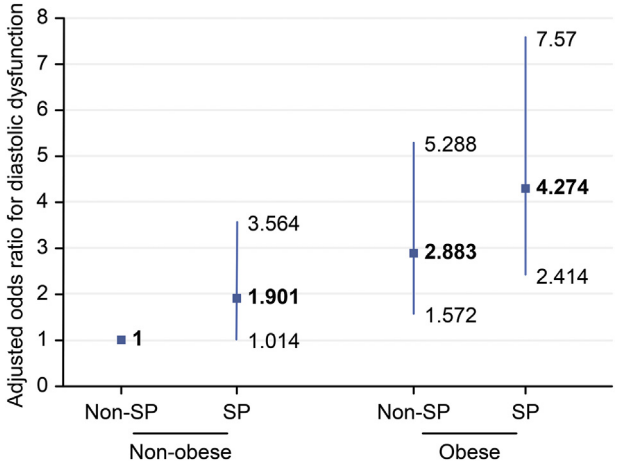

Fig. 3. Risk of diastolic dysfunction based on sarcopenia/obesity group. Note the gradual increase in risk across sarcopenia/obesity group. The deleterious effect of sarcopenia was additive to obesity. Obesity combined with sarcopenia conferred a higher risk for diastolic dysfunction than the other phenotypes, including non-sarcopenic obese subjects, independent of age, sex, and other possible confounders. SP; sarcopenia.

It is well known that obesity elevates the risk of heart failure, particularly HFpEF, in a dose-dependent manner [27–29]. Bello et al. previously demonstrated that obesity measurements were associated with adverse LV remodeling and subclinical LV systolic and diastolic function in the Atherosclerosis Risk in Communities (ARIC) cohort [11]. Interestingly, these abnormalities were more evident in females and were corroborated in our study. These findings of a closer relationship between body measurements and LV function in females might partially explain the female predominance of HFpEF.

Interestingly, we observed that a certain subset of obese subjects (those with sarcopenia) had more profound LV diastolic dysfunction and decreased exercise capacity. This observation indicated that not all obese subjects have a similar elevated risk for HFpEF, suggesting heterogeneity of the obese group (partially related to the obesity paradox) [1,27,29–31]. In this study, we found that sarcopenia, per se, also adversely affected LV diastolic function, regardless of other confounding factors. Furthermore, the deleterious effects of sarcopenia and obesity were additive, suggesting that maintaining an appropriate muscle mass may play a protective role in obese subjects [32–35]. Taken together, our findings underscore the importance of measuring body composition in addition to overall obesity to identify obese subjects who are more susceptible to developing HFpEF [11,30]. Furthermore, sarcopenia could be an important target for preventing HFpEF in obese subjects. Considering the refractoriness of current medications for HFpEF, focusing on primary prevention by targeting obesity and sarcopenia might currently be the best treatment strategy [31–37]. In a community setting, Villareal et al. demonstrated that a combination of diet control and exercise training was superior to diet control alone for improving functional status in elderly obese populations [37]. Intriguingly, among different exercise modes, combined aerobic and resistance exercise resulted in the greatest benefit to physical function, which was accompanied by attenuated muscle mass loss, improved strength, and increased exercise capacity compared with single exercise modes (either aerobic or resistance exercise). This observation partly supports the efficacy of muscle-preserving exercise as a primary prevention strategy in the general population. Additional research is needed to clarify the effectiveness of lifestyle modification, such as physical activity and nutritional care, for the primary prevention of HFpEF.

Lastly, we confirmed that exercise intolerance (a main symptom of HFpEF) varied among the different sarcopenia/obesity groups. Due to the cross-sectional nature of this study, we do not provide direct evidence that different sarcopenia/obesity groups would indeed differentially develop HFpEF. However, evaluating the different exercise capacities according to sarcopenia/obesity group could provide further evidence of a connection between these phenotypes and the risk of HFpEF.

Several limitations of our study should also be discussed. First, as we previously mentioned, this was a cross-sectional study; thus, our conclusion should be considered for hypothesis generation, and additional longitudinal and/or interventional studies are needed. Second, inconsistencies in defining sarcopenia exist in the literature [38–42]. Thus, the characteristics and consequences of sarcopenia might differ according to the method used to define sarcopenia. We additionally performed analyses with more stringent criteria for sarcopenia (class II sarcopenia, defined as 2 standard deviations below the mean of the young reference group) [21]. Overall, the results were similar to those of the main analysis (supplementary Tables A.3 and A.4). Third, selection bias might have existed, as the included participants represented a highly educated, high-income population of subjects who were proactive regarding their health and wellness and could afford comprehensive health check-ups. Fourth, our study population was exclusively performed among Koreans, and the cut-off BMI value applied in the current study [20] might be inappropriate for other Asian countries or other ethnicities [43]. Furthermore, body composition and metabolic characteristics might be different between Asian and Western populations [44,45]. Thus, our findings cannot be extrapolated to non-Korean populations. Lastly, in clinical practice, those with comorbidities (e.g., proven cardiovascular diseases, structural heart disease, lung disease, anemia, diabetes, and hypertension) frequently have either sarcopenia or obesity [6]. Thus, the exclusion of those with comorbidities might have led to limited numbers in both the sarcopenia and obese groups, further limiting its clinical application. However, to identify the independent

Table 4
Risk for diastolic dysfunction according to obesity and sarcopenia.

Presence of obesity	Non-obese	Obese	p value
Unadjusted OR (95% CI)	1 (ref.)	2.354 (1.647–3.363)	<0.001
Adjusted OR (95% CI)			
Model 1[a]	1 (ref.)	3.573 (2.316–5.511)	<0.001
Model 2[b]	1 (ref.)	3.039 (1.922–4.804)	<0.001
Presence of SP	**Non-SP**	**SP**	**p value**
Unadjusted OR (95% CI)	1 (ref.)	3.180 (2.210–4.575)	<0.001
Adjusted OR (95% CI)			
Model 1[a]	1 (ref.)	2.421 (1.632–3.590)	<0.001
Model 2[b]	1 (ref.)	2.250 (1.445–3.505)	<0.001

CI, confidence interval; OR, odds ratio; SP, sarcopenia.
[a] p value after adjustment for age and sex.
[b] p value after adjustment for age, sex, systolic blood pressure, heart rate, left ventricular mass index, high density lipoprotein cholesterol, and HOMA-IR.

Table 5
Sex-specific risk for diastolic dysfunction according to SP/obesity category.

Female	Non-SP/non-obese	SP/non-obese	Non-SP/obese	SP/obese
Unadjusted OR (95% CI)	1 (ref.)	3.529 (1.813–6.872)	5.020 (1.285–19.608)	7.798 (3.777–16.102)
Adjusted OR (95% CI)				
Model 1[a]	1 (ref.)	2.496 (1.219–5.110)	7.149 (1.660–30.795)	5.568 (2.521–12.297)
Model 2[b]	1 (ref.)	2.532 (1.204–5.324)	4.997 (1.099–22.722)	5.986 (2.599–13.787)
Male	Non-SP/non-obese	SP/non-obese	Non-SP/obese	SP/obese
Unadjusted OR (95% CI)	1 (ref.)	2.778 (0.697–11.073)	2.410 (1.338–4.342)	3.876 (1.930–7.785)
Adjusted OR (95% CI)				
Model 1[a]	1 (ref.)	0.933 (0.190–4.593)	3.209 (1.676–6.145)	4.056 (1.882–8.744)
Model 2[b]	1 (ref.)	0.708 (0.139–3.592)[c]	2.568 (1.308–5.040)	3.199 (1.460–7.013)

CI, confidence interval; OR, odds ratio; SP, sarcopenia.
[a] p value after adjusting for age.
[b] p value after adjusting for the age, systolic blood pressure, heart rate, left ventricular mass index, high-density lipoprotein cholesterol, and HOMA-IR.
[c] This finding may be due to the lower prevalence among the SP/non-obese group (2.8% of all male) and may not be suggestive of an actual lower risk in the SP/non-obese group.

roles of obesity and sarcopenia on LV dysfunction, we extensively excluded those patients and adjusted for various confounders (e.g., age, sex, degree of LV hypertrophy, level of systolic BP, and insulin resistance). Our results remained robust after implementing these steps. To the best of our knowledge, this is the first report to explore the combined effect of sarcopenia and obesity on LV function and exercise capacity.

5. Conclusion

In a general healthy population without overt cardiovascular disease, we observed that sarcopenic obesity was associated with worse diastolic function and exercise capacity. Interestingly, among obese individuals, the risk of diastolic dysfunction differed according to the presence of sarcopenia, which was stronger in females. The present study highlights the importance of measuring body composition in the reclassification of obese populations and implies the possibility that both obesity and sarcopenia could be targets for the prevention of HFpEF in the general population.

Authors' contributions

MHJ, SHI, SMP, HOJ, KSH, SHB, and HJY contributed to the conception or design of the work. MHJ and SHI contributed to the acquisition, analysis, or interpretation of the data. MHJ drafted the manuscript. SHI, SMP, HOJ, KSH, SHB, and HJY critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.05.007.

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