Title: Mitral Systolic Velocity at Peak Exercise Predicts Impaired Exercise Capacity in Patients with Heart Failure with Preserved Ejection Fraction

Running title: A predictor of exercise capacity in heart failure

Kenji Masada, MD; Takayuki Hidaka, MD, PhD; Yuu Harada, MD; Mirai Kinoshita, MD; Kiho Itakura, MD; Akifumi Higashi, MD; Hiroto Utsunomiya, MD, PhD; Yasuki Kihara, MD, PhD

Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Science, Hiroshima, Japan

Address for correspondence:

Takayuki Hidaka, MD, PhD,

Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Telephone: +81-82-257-5540

Fax: +81-82-257-1543

Email: hida-taka@umin.ac.jp

Abstract

Background

Nearly half patients with heart failure have normal left ventricular ejection fraction (LVEF), but their prognosis is no better than those with reduced LVEF. Although peak oxygen consumption (VO_2) is an independent predictor of mortality in heart failure, it is unclear how cardiac function during exercise contributes to peak VO_2. Therefore, we explored the useful parameters measured by exercise stress echocardiography to predict peak VO_2 in patients with heart failure with preserved LVEF (HFpEF).

Methods and results

We assessed 80 patients being investigated for effort intolerance or dyspnea, and finally analyzed 50 patients who satisfied the HFpEF criteria. Mean peak VO_2 was 16.4 ± 2.8 ml/kg/min. Twenty-three patients (46.0%) achieved a peak VO_2 <16.0 ml/kg/min (Weber class C or D). There was a significant relationship between mitral systolic velocity (S') and cardiac output (CO) at rest ($R = 0.55$, $P < 0.0001$) and peak exercise ($R = 0.64$, $P < 0.0001$). The absolute increase in S' from rest to peak exercise also correlated with the absolute increase in CO ($R = 0.32$, $P = 0.02$). Multivariate logistic regression analysis showed that S' at peak exercise independently predicted

peak VO_2. Receiver-operator characteristic curve analysis identified that an S' at peak exercise of ≤8.13 cm/s predicted a peak VO_2 <16.0 ml/kg/min (sensitivity 95.7%, specificity 44.4%, area under curve 0.70, 95% confidence interval 0.55–0.84, P = 0.004).

Conclusions

Mitral systolic velocity at peak exercise accurately reflects peak VO_2, and may facilitate stratification of risk in patients with HFpEF.

Key words: heart failure; exercise tolerance; exercise echocardiography; tissue Doppler echocardiography; mitral annular velocity.

Introduction

Nearly half patients presenting with symptoms and signs of heart failure (HF) are reported to have normal left ventricular ejection fraction (LVEF), but mortality and morbidity are similar to those of patients with HF with reduced LVEF.[1] The pathophysiology of HF with preserved LVEF (HFpEF) is characterized by diastolic dysfunction, impaired systolic function, aortic stiffening, abnormal ventricular-arterial coupling, chronotropic incompetence, and underlying diseases such as hypertension and diabetes mellitus.[2-8] Patients with HFpEF most commonly complain of breathlessness during exercise. Exercise stress echocardiography (ESE) and cardiopulmonary exercise testing (CPET) have been used to demonstrate the pathophysiology of HFpEF.[9-16] Peak oxygen consumption (VO_2) on CPET is a well-established and independent predictor of mortality in patients with HF, including those with HFpEF,[17-20] and there is reportedly a relationship between peak VO_2 and parameters measured by rest echocardiography (RE) in patients with HFpEF.[10,21] Nevertheless, the relationship between peak VO_2 and the parameters measured by ESE are not completely understood. We hypothesized that parameters measured by ESE would be more closely related to peak VO_2 than those of RE, as peak VO_2 reflects exercise tolerance. We performed a study to investigate the relationship between peak

VO_2 and ESE parameters in patients with HFpEF, using ESE combined with CPET (ESE-CPET).

Methods

Study population

We enrolled patients with LVEF >50% who had been referred for investigation of effort intolerance or dyspnea. The diagnosis of HFpEF was made in those: with normal LVEF (>50%); who fulfilled the criteria for New York Heart Association functional class II or III; and had abnormal diastolic function (indeterminate or diastolic dysfunction)[22] and/or a history of hospitalization for congestive heart failure (CHF). Hypertensive patients matched for age and sex without symptoms and signs of HF were also recruited as control in this study period. Exclusion criteria were significant aortic or mitral valve stenosis, congenital heart disease, infiltrative or hypertrophic obstructive cardiomyopathy, pericardial constriction, presence of a pacemaker or implantable cardiac defibrillator, chronic pulmonary disease requiring home oxygen therapy, severe renal dysfunction, uncontrolled hypertension despite medical therapy and an inability to exercise. Participants took their normal drugs on the day of ESE-CPET. The research protocol was approved by our institutional ethics committee. All patients provided written informed consent to participate.

Cardiopulmonary exercise testing and laboratory tests

Patients performed ESE with concurrent ventilator expired gas analysis on a supine bicycle ergometer (Road, Echo Stress Table 750EC, Groningen, The Netherlands) capable of tilting to the left lateral position. Patients pedaled at a constant cadence (50 rotations/min), starting with an initial workload of 10 W for 3 minutes, which was then increased by 10 W/min (ramp protocol). During the test, the 12-lead electrocardiogram and heart rate were continuously monitored and blood pressure was measured every minute. The test was terminated if signs of severe distress or myocardial strain were observed, or if a patient reached their maximal level of physical exertion. We measured some parameters on a breath-by-breath basis using a gas analysis technique (MINATO 280S; Minato Ikagaku, Osaka, Japan). We also took a venous blood sample for routine laboratory analysis and measurement of serum N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration.

Rest and exercise stress echocardiography

Two experienced clinicians performed RE and ESE using a Vivid E9 ultrasound system with a 2.5-MHz transducer (GE Vingmed Ultrasound, Horten, Norway). All imaging data were digitized and saved on an optical disc for off-line analysis (Echo Pac software version 112, GE Vingmed Ultrasound). All echocardiographic measurements were

taken according to the recommendations of the American Society of Echocardiography[23] by an experienced sonographer without knowledge of the patients' clinical status. All parameters were measured in triplicate and averaged. Rest standard 2-dimensional, M-mode and Doppler blood flow recordings were performed using standard methods.[23] Peak early diastolic filling (E) and late diastolic filling (A) velocities and the E/A ratio were measured from transmitral flow. Tissue Doppler images of movement of the mitral annulus were obtained from the apical four-chamber view. A sample volume was placed at the septal and lateral annular sites. Analysis was performed for the early (E') diastolic peak velocity and systolic (S') peak velocity. The E/E' ratio, E' diastolic peak velocity and S' peak velocity were calculated using the averaged values from the septal and lateral sites. The LV mass index and relative wall thickness were calculated by standard methods.[23] Right atrial (RA) pressure was estimated by the inferior vena cava diameter and its response to inspiration.[23] Pulmonary artery systolic pressure (PASP) was estimated using the modified Bernoulli formula ($4 \times$ [tricuspid regurgitation velocity (TRV) at end-expiration]^2) + RA pressure.[23] Exercise stress echocardiographic images were acquired at rest and peak stress. Analysis parameters were the E and A velocities, the E/A ratio, E' diastolic peak velocity, S' peak velocity, the E/E' ratio and left ventricular out flow tract-velocity time integral (LVOT-VTI). Stroke volume (SV) was calculated by using the aortic valve

pulsed wave Doppler method, whereby LVOT-VTI was multiplied by the area of the aortic annulus. Cardiac output (CO) was calculated from the product of SV and heart rate (HR). Effective arterial elastance (Ea) was also calculated at rest and peak stress according to the following equation:[8,24]

$$Ea = 0.9 \times \text{systolic blood pressure} / SV$$

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or number (proportion, %). Categorical variables were compared by use of Pearson's chi-square test or Fisher exact test. Comparisons between patients with HFpEF and control subjects were performed using Student's unpaired t-test. The paired t-test was used to compare rest and peak stress parameters. The repeated measures linear model analysis was used to define the within-group effect for each parameter over time, the between-group differences over time, and the time-by-group interactions. The relationship between S' and CO during exercise was examined using the Pearson correlation coefficient. Multivariate linear regression was undertaken to assess independent correlations with peak VO_2 using clinically relevant, significant variables from the univariate model. Receiver-operator characteristic (ROC) curves were plotted to determine the sensitivity and specificity of S' at peak exercise and the E/E' ratio at

rest, in order to predict peak VO_2 <16.0 ml/kg/min. A P value <0.05 was considered to be statistically significant. Data were analyzed using JMP statistical software for Windows (version 12.0, SAS Institute Inc., Cary, NC, USA).

Results

We assessed 80 consecutive patients: ultimately 57 were enrolled as they satisfied the criteria for HFpEF, and 7 were excluded either because of atrial fibrillation (n = 5) or because the echocardiographic images were not suitable for analysis (n = 2). Table 1 provides a summary of the baseline demographic and clinical characteristics of the 50 patients with HFpEF (40.0% were female, mean age 67 years ± 9 years) and 10 control subjects. Forty-five patients with HFpEF (90.0%) had hypertension, and 17 (34.0%) had ever been hospitalized for CHF. Furthermore, patients with HFpEF had higher log NT-proBNP serum levels (5.1 ± 1.3 vs 3.8 ± 0.8, P = 0.005), and were more likely to be taking beta-adrenoreceptor blockers (46.0% vs 10.0%, P = 0.03) than control subjects.

Rest echocardiography

The RE parameters are shown in Table 2. The RE parameters of patients with HFpEF having had larger or higher than control subjects were: left ventricular dimension in systole index (2.0 ± 0.3 vs 1.7 ± 0.2 cm/m^2, P = 0.02), left atrial volume index (42.2 ± 14.1 vs 27.1 ± 4.5 ml/m^2, P = 0.002), LV mass index (97.0 ± 27.0 vs 73.1 ± 21.9 g/m^2 , P = 0.01), the E/E' ratio (12.8 ± 3.2 vs 10.0 ± 1.7, P = 0.009), and PASP (19.1 ± 12.0 vs 8.7 ± 9.3 mmHg, P = 0.01).

Exercise stress echocardiography combined with cardiopulmonary exercise testing

The parameters measured by ESE-CPET are shown in Table 3. All parameters except for the E/A ratio in patients with HFpEF, as well as PASP and diastolic blood pressure in control subjects changed significantly from rest to peak exercise. Patients with HFpEF had lower S' at peak (7.5 ± 1.4 vs 8.8 ± 0.9 cm/s, P = 0.007), higher the E/E' ratio at rest (12.8 ± 3.2 vs 10.0 ± 1.7, P = 0.009), higher PASP at rest (19.1 ± 12.0 vs 8.7 ± 9.3 mmHg, P = 0.01) and peak (25.9 ± 19.1 vs 8.9 ± 12.1 mmHg, P = 0.02) , lower peak VO_2 (16.4 ± 2.8 vs 18.4 ± 2.3 mmHg, P = 0.04), and lower respiratory exchange ratio (1.17 ± 0.12 vs 1.28 ± 0.10, P = 0.008) than control subjects. The ESE-CPET parameters which significantly differed as time-by-group interactions between the groups were: E wave (P = 0.002), S' (P = 0.01), and VO_2 (P = 0.03). Among the ESE-CPET parameters at peak exercise, A wave, E', and PASP could not be measured in all patients (Table 3). Twenty-three (46.0%) patients with HFpEF achieved a peak VO_2 <16.0 ml/kg/min (Weber class C or D).[17,25] None of the patients developed chest pain, and no ST segment changes indicative of myocardial ischemia were observed in any patient during ESE-CPET.

Relationship between mitral systolic velocity and cardiac output

The relationship between S' and CO in patients with HFpEF is shown Figure 1; there was a significant relationship between S' and CO at rest (R = 0.55, P < 0.0001) and peak exercise (R = 0.64, P <0.0001). The absolute increase in S' from rest to peak exercise also correlated significantly with the absolute increase in CO (R = 0.32, P = 0.02).

Univariate and multivariate analyses for peak oxygen consumption

The results of univariate and multivariate analyses to assess the relationships between peak VO_2 and the variables measured by ESE-CPET in patients with HFpEF are shown in Table 4, 5. The ESE-CPET variables significantly related to peak VO_2 on univariate analysis were: log NT-proBNP (R = -0.41, P = 0.004), S' at rest (R = 0.40, P = 0.004), S' at peak exercise (R = 0.46, P = 0.0009), the E/E' ratio at rest (R = -0.31, P = 0.03), SV at rest (R = 0.29, P = 0.04), CO at peak exercise (R = 0.39, P = 0.008), and Ea at rest (R = -0.32, P = 0.02). There appeared to be strong relationships between S' at rest and SV at rest (R = 0.57, P < 0.0001), and between S' at peak exercise and CO at peak exercise (R = 0.64, P <0.0001), so we chose S' at rest and peak exercise for the multivariate analysis. The multivariate regression analysis showed that S' at peak exercise and the E/E' ratio at rest were independent predictors of peak VO_2. There was

a strong correlation between S' at rest and S' at peak exercise (R = 0.80, P <0.0001), so these parameters were not included in multivariate analysis together. According to the ROC curve analysis, a value of S' at peak exercise ≤8.13 cm/s was the best predictor of a peak VO_2 <16.0 ml/kg/min (sensitivity 95.7%, specificity 44.4%, area under curve [AUC] 0.70, 95% confidence interval [CI] 0.55–0.84, P = 0.004). The E/E' ratio at rest was not a useful parameter (AUC 0.60; 95% CI 0.44–0.76, P = 0.26) (Figure 2).

Discussion

To the best of our knowledge, ours is the first study to have investigated the relationship between peak VO_2 and parameters measured by ESE in patients with HFpEF. Our major findings were that S' at peak exercise and the E/E' ratio at rest were independent predictors of peak VO_2, and that S' at peak exercise is a sensitive way of identifying patients with HFpEF impaired exercise capacity. Taking into account the strong relationship between peak VO_2 and mortality, we recommend that measuring S' at peak exercise should become a part of routine clinical practice.

Mitral systolic velocity

We found that S' at peak exercise was an independent predictor of peak VO_2 in patients with HFpEF. Peak VO_2 is determined by three of the variables in the Fick equation thus:

$$\text{Peak } VO_2 = (SV_{peak} \times HR_{peak}) \times AVO_2$$

where AVO_2 is the difference between arterial oxygen content and venous oxygen content.

An impaired CO response in patients with HF correlates significantly with reductions in peak VO_2,[26] and CO is thought to be the chief determinant of VO_2. We found that CO

at peak exercise correlated strongly with peak VO_2. Cardiac output is the product of SV and HR. Kitzman et al.[27] reported that SV augmentation during exercise was impaired in patients with HFpEF, and consequently HR increased to maintain CO and compensate for the inadequate SV response. Other non-invasive studies have also demonstrated similar hemodynamic responses to exercise in patients with HFpEF.[9,11,12,16] Of the parameters measured by ESE that we found significantly correlated with peak VO_2, S' at peak exercise was most closely correlated with CO at peak exercise. Moreover, S' at rest and the absolute increase in S' from rest to peak exercise were also significantly correlated with CO at rest and the absolute increase in CO. We judge that S' accurately reflects CO during exercise in patients with HFpEF. It has been reported that S' is the accurate reflection of LV longitudinal systolic function that can be obtained with tissue Doppler imaging.[5,28] Although it is recognized that there is a strong relationship between LV global longitudinal strain and peak VO_2 in patients with HFpEF,[10] it has not been clear how LV longitudinal systolic function during exercise contributes to CO response and peak VO_2. Our findings demonstrate that LV longitudinal systolic function during exercise assessed by S' significantly correlated with CO response, as SV augmentation combined with a HR response to maximize VO_2. In our opinion, S' at peak exercise is a valuable means of assessing exercise capacity in patients with HFpEF.

Mitral inflow to mitral relaxation velocity ratio

The E/E' ratio at rest was also an independent predictor of peak VO_2. Previous reports have demonstrated the relationship between peak VO_2 and the E/E' ratio at rest.[10,21] It has been reported that an elevated E/E' ratio at rest correlated with an elevated mean pulmonary capillary wedge pressure and an elevated LV end diastolic pressure.[22,29] High resting filling pressure is associated with impaired exercise capacity.[11] In our study, the E/E' ratio at peak exercise did not correlate with peak VO_2. None of the previous studies have examined the influence of the change in filling pressure brought about by exercise on exercise capacity. High LV filling pressure during exercise is frequently considered to be a cause of dyspnea, but conclusive evidence for this hypothesis remains elusive. Further studies are needed to clarify the relationship between LV filling pressure during exercise and exercise tolerance in patients with HFpEF.

Impaired exercise capacity in patients with HFpEF

Peak VO_2 is recognized as a strong predictor of mortality in patients with HFpEF.[17-20] Peak VO_2 <16.0 ml/kg/min (Weber class C or D) reflects more severe HF and carries a worse prognosis.[17,25] We found that S' at peak exercise and the E/E' ratio at rest were

independent predictors of peak VO_2, but our ROC curve analysis revealed that S' at peak exercise was the only sensitive means of identifying patients with HFpEF with peak VO_2 <16.0 ml/kg/min. In our opinion, S' at peak exercise is also a potentially valuable means of identifying patients with HFpEF at high risk of morbidity and mortality.

Clinical implications

Our study provides evidence that S' during exercise is a useful parameter to reflect CO response and identify high risk patients with HFpEF impaired exercise capacity.

The measurement of S' at rest and during exercise was straightforward in all patients. In clinical practice, S' is easier to measure than CO, even when the aortic valve pulsed wave Doppler method is used. If CPET equipment is not available, we recommend measuring S' at peak exercise as a reflection of exercise capacity of patients with HFpEF.

Limitations

Our study had some limitations. First, our sample consisted of a small number of patients from a single center in Japan. Patients with HFpEF in our study had lower body surface area and body mass index (BMI) than those in previous reports. In

general, the prevalence of obesity is lower in Asian populations than Westerners. Consistent with our results, BMI was relatively low in patients with HFpEF researched in Japan.[30] Therefore, our results must be confirmed in a prospective study with a larger number of patients in other foreign countries. Second, all patients took their normal cardiac drugs on the day of ESE-CPET, as it was considered unethical to stop treatment entirely. Consequently, beta-adrenoreceptor blockers and calcium channel blockers may have influenced HR response. Third, among the ESE-CPET parameters at peak exercise, A wave, E', and PASP could not be measured in all patients. A wave and E' at peak exercise were not easy parameters to determine because of merging of E and A velocities, and E' and the late diastolic peak velocity due to sinus tachycardia (ST). TRV at peak exercise was an also difficult parameter to determine due to ST and tachypnea. In our study, PASP at peak exercise in patients with HFpEF was the lowest feasible parameter of ESE-CPET. The reduced feasibility of parameters at peak exercise is one of the major limitations of ESE. It might have influenced our data. Finally, an S' at peak exercise of ≤8.13 cm/s predicted a peak VO_2 <16.0 ml/kg/min with high sensitivity but low specificity. There was the potential for an increase of having false-positive cases, but it was suitable for screening of high risk patients with HFpEF because of high sensitivity. We think that S' at peak exercise is a useful parameter in clinical practice to facilitate stratification of risk in patients with

HFpEF impaired exercise capacity.

Conclusions

Mitral systolic velocity at peak exercise accurately reflects peak VO_2, and is a useful means of screening high risk patients with HFpEF impaired exercise capacity. Consideration should be given to measuring S' at peak exercise in patients with HFpEF as a part of routine clinical exercise.

References

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-869.
2. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure-abnormalities in active relaxation and passive stiffness of the left ventricle. New Engl J Med 2004;350:1953-1959.
3. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714-720.
4. Hundley WG, Kitzman DW, Morgan TM et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 2001;38:796-802.
5. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic

abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195-1201.

6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. New Engl J Med 2006;355:251-259.

7. Borlaug BA, Melenovsky V, Russell SD et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138-2147.

8. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005;111:2306-2312.

9. Tan YT, Wenzelburger F, Lee E et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36-46.

10. Hasselberg NE, Haugaa KH, Sarvari SI, et al. Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. Eur Heart J Cardiovasc Imaging 2015;16:217-224.

11. Penicka M, Bartunek J, Trakalova H et al. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: a pressure-volume loop analysis. J Am Coll Cardiol 2010;55:1701-1710.

12. Tartiere-Kesri L, Tartiere JM, Logeart D, Beauvais F, Cohen Solal A. Increased proximal arterial stiffness and cardiac response with moderate exercise in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol 2012;59:455-461.

13. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol 2010;56:855-863.

14. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 2011;58:265-274.

15. Borlaug BA, Olson TP, Lam CS et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 2010;56:845-854.

16. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail 2013;15:776-785.

17. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Eur Heart J 2012;33:2917-2927.

18. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. J Am Coll Cardiol 2005;46:1883-1890.

19. Shafiq A, Brawner CA, Aldred HA, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. Am Heart J 2016;174:167-172.

20. Gitt AK, Wasserman K, Kilkowski C et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 2002;106:3079-3084.

21. Arruda AL, Pellikka PA, Olson TP, Johnson BD. Exercise capacity, breathing pattern, and gas exchange during exercise for patients with isolated diastolic dysfunction. J Am Soc Echocardiogr 2007;20:838-846.

22. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of

Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.

23. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;16:233-270.

24. Kelly RP, Ting CT, Yang TM, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513-521.

25. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213-1223.

26. Higginbotham MB, Morris KG, Conn EH, Coleman RE, Cobb FR. Determinants of variable exercise performance among patients with severe left ventricular dysfunction. American J Cardiol 1983;51:52-60.

27. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991;17:1065-1072.

28. Ha JW, Lee HC, Kang ES, et al. Abnormal left ventricular longitudinal functional reserve in patients with diabetes mellitus: implication for detecting

subclinical myocardial dysfunction using exercise tissue Doppler echocardiography. Heart 2007;93:1571-1576.

29. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-1794

30. Obokata M, Takeuchi M, Negishi K et al. Relation Between Echocardiogram-Based Cardiac Parameters and Outcome in Heart Failure With Preserved and Reduced Ejection Fraction. The American journal of cardiology 2016;118:1356-1362.

Figure legends

Figure 1. Relationship between mitral systolic velocity (S') and cardiac output (CO) at rest and peak exercise, and absolute increases from rest to peak exercise (Δ).

Figure 2. Receiver-operating characteristic curve analysis using mitral systolic velocity (S') at peak exercise and the mitral inflow to mitral relaxation velocity ratio (E/E') at rest to identify patients with heart failure with preserved ejection fraction impaired peak oxygen consumption <16.0 ml/min/kg. Other abbreviations: AUC, area under the curve; CI, confidence interval.

Figure 1

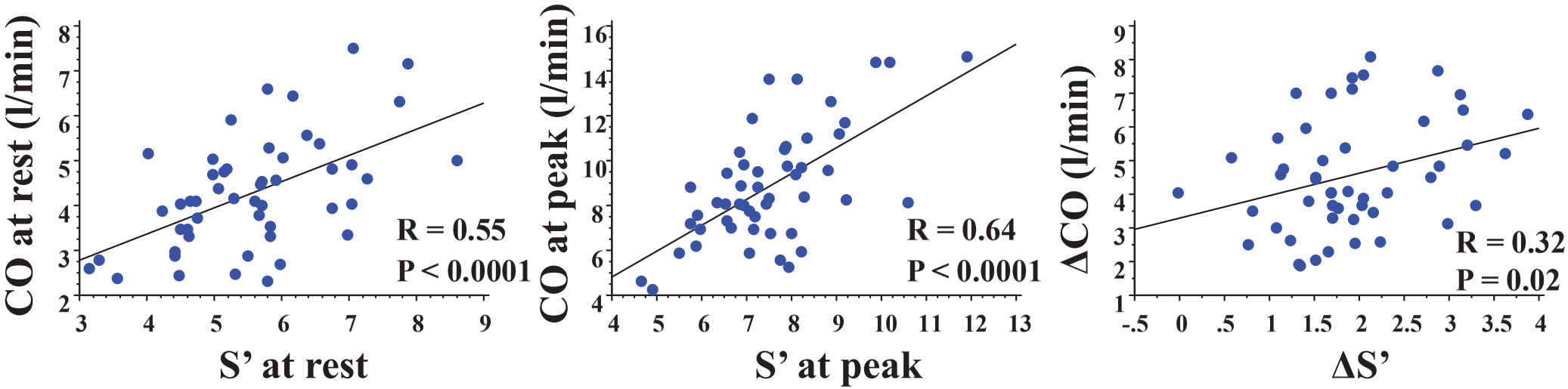
CO at rest (l/min)
S' at rest
R = 0.55
P < 0.0001
CO at peak (l/min)
S' at peak
R = 0.64
P < 0.0001
ΔCO (l/min)
ΔS'
R = 0.32
P = 0.02

Figure 2

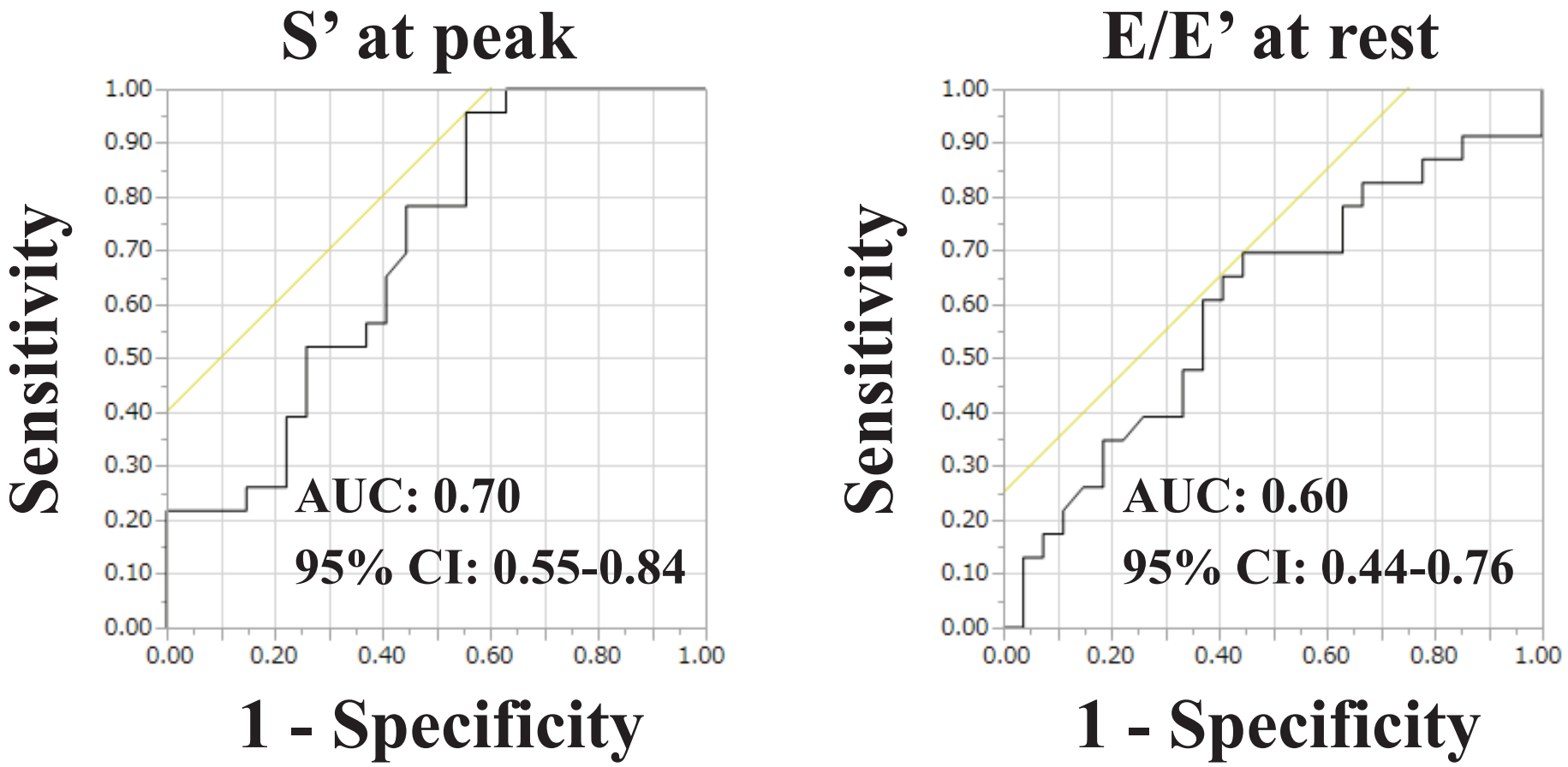
S' at peak
Sensitivity
1 - Specificity
AUC: 0.70
95% CI: 0.55-0.84
E/E' at rest
Sensitivity
1 - Specificity
AUC: 0.60
95% CI: 0.44-0.76

Table 1. Baseline Clinical Characteristics

Valiables	HFpEF (n = 50)	Control (n = 10)	P value
Age, years	67 ± 9	68 ± 4	NS
Females, (%)	20 (40)	4 (40)	NS
BSA, m^2	1.67 ± 0.23	1.70 ± 0.10	NS
BMI, kg/m^2	23.9 ± 4.6	24.1 ± 2.4	NS
NYHA class, n (%)			
Ⅱ	33 (66)	-	
Ⅲ	17 (34)	-	
Hypertension, n (%)	45 (90)	10 (100)	NS
Diabetes, n (%)	19 (38)	3 (30)	NS
Smoking, n (%)	29 (58)	6 (60)	NS
History of hospitalization for CHF	17 (34)	0 (0)	0.04
Hemoglobin, g/dl	13.2 ± 1.7	14.3 ± 0.9	NS
Creatinine, mg/dl	0.9 ± 0.3	1.0 ± 0.1	NS
Hemoglobin A_1c, g/dl	6.0 ± 0.9	6.3 ± 0.7	NS
NT-proBNP, pg/ml	385.1 ± 644.3 (n =49)	61.0 ± 55.6	NS
Log NT-proBNP	5.1 ± 1.3 (n =49)	3.8 ± 0.8	0.005
Medications, n (%)			
β-blockers	23 (46)	1 (10)	0.03
ACE inhibitors/ARAs	34 (68)	6 (60)	NS
Calcium channel blockers	18 (36)	2 (20)	NS
Diuretic	12 (27)	1 (10)	NS

Values are presented as mean ± SD or n (%); BSA, body surface area; BMI, body mass index.
CHF, congestive heart failure; NYHA, New York Heart Association.
NT-proBNP, N-terminal pro-B-type-natriuretic peptide; ACE, angiotensin-converting enzyme.
ARA, angiotensin receptor antagonist.

Table 2. Rest echocardiography

Valiables	HFpEF (n = 50)	Control (n = 10)	P value
Aortic annulus, cm	2.0 ± 0.2	2.1 ± 0.1	NS
LAD, cm	3.9 ± 0.6	3.5 ± 0.5	NS
IVS, cm	0.9 ± 0.2	0.9 ± 0.1	NS
PW,cm	1.0 ± 0.2	0.9 ± 0.1	NS
LVDdI, cm/m^2	3.0 ± 0.5	2.7 ± 0.3	NS
LVDsI, cm/m^2	2.0 ± 0.3	1.7 ± 0.2	0.02
LAVI, ml/m^2	42.2 ± 14.1	27.1 ± 4.5	0.002
> 34.0, n (%)	39 (78)	0 (0)	< 0.0001
LVEDVI, ml/m^2	49.8 ± 13.4	42.6 ± 7.5	NS
LVESVI, ml/m^2	19.4 ± 6.6	15.6 ± 2.6	NS
LVEF, %	61.4 ± 4.8	63.2 ± 2.6	NS
LVMI, g/m^2	97.0 ± 27.0	73.1 ± 21.9	0.01
LV hypertrophy, n (%)	15 (30)	0 (0)	0.04
RWT	0.39 ± 0.07	0.38 ± 0.04	NS
E wave, cm/s	74.7 ± 16.1	64.6 ± 12.6	NS
A wave, cm/s	68.5 ± 19.2	80.3 ± 9.3	NS
E/A	1.21 ± 0.67	0.80 ± 0.11	NS
E', cm/s	6.3 ± 1.7	6.6 ± 1.0	NS
S', cm/s	5.6 ± 1.2	6.1 ± 1.1	NS
E/E'	12.8 ± 3.2	10.0 ± 1.7	0.009
> 14.0, n (%)	19 (38)	0 (0)	0.02
LVOT-VTI, cm	20.7 ± 5.8	19.4 ± 2.3	NS
PASP, mmHg	19.1 ± 12.0	8.7 ± 9.3	0.01
PA acceleration time, ms	129.1 ± 24.1	126.9 ± 26.6	NS

LAD, left arterial dimention; IVS, interventricular septum; PW, posterior wall.
LVDdI, left ventricular dimension in diastole index.
LVDsI, left ventricular dimension in systole index; LAVI, left atrial volume index.
LVEDVI, left ventricular end-diastolic volume index.
LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction.
LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.
RWT, relative wall thickness; E wave, early mitral diastolic inflow velocity.
A wave, late mitral diastolic inflow velocity; E/A, early to late mitral inflow velocities ratio.
E', mitral relaxation velocity; S', mitral systolic velocity.
E/E', mitral inflow to mitral relaxation velocity ratio.
LVOT-VTI, left ventricular out flow tract-velocity time integral.
PASP, pulmonary artery systolic pressure.

Table3. Exercise stress echocardiography combined with cardiopulmonary exercise testing

Valiables	HFpEF (n = 50)	Within Group	Control (n = 10)	Within Group	Between Groups	Time-Group Interaction
E wave, cm/s						
Rest	74.7 ± 16.1	< 0.0001	64.6 ± 12.6	< 0.0001	NS	0.002
Peak	109.5 ± 21.0		121.6 ± 16.9		NS	
A wave, cm/s						
Rest	68.5 ± 19.2	< 0.0001	80.3 ± 9.3	0.005	NS	NS
Peak	91.8 ± 29.3 (n = 42)		104.2 ± 20.3 (n = 7)		NS	
E/A						
Rest	1.21 ± 0.67	NS	0.80 ± 0.11	0.03	NS	NS
Peak	1.32 ± 0.56 (n = 42)		1.16 ± 0.36 (n = 7)		NS	
S', cm/s						
Rest	5.6 ± 1.2	< 0.0001	6.1 ± 1.1	< 0.0001	NS	0.01
Peak	7.5 ± 1.4		8.8 ± 0.9		0.007	
E', cm/s						
Rest	6.3 ± 1.7	< 0.0001	6.6 ± 1.0	0.0002	NS	NS
Peak	8.2 ± 2.1 (n = 45)		9.3 ± 1.3 (n = 9)		NS	
E/E'						
Rest	12.8 ± 3.2	0.007	10.0 ± 1.7	0.007	0.009	NS
Peak	14.6 ± 5.3 (n = 45)		13.5 ± 2.0 (n = 9)		NS	
PASP, mmHg						
Rest	19.1 ± 12.0	< 0.0001	8.7 ± 9.3	NS	0.01	NS
Peak	25.9 ± 19.1 (n = 34)		8.9 ± 12.1 (n = 9)		0.02	
LVOT-VTI, cm						
Rest	20.7 ± 5.8	< 0.0001	19.4 ± 2.3	< 0.0001	NS	NS
Peak	23.5 ± 4.7		23.0 ± 2.7		NS	
Stroke volume, ml						
Rest	65.3 ± 17.9	< 0.0001	66.2 ± 10.9	< 0.0001	NS	NS
Peak	75.3 ± 19.8		79.2 ± 17.2		NS	
Cardiac output, l/min						
Rest	4.3 ± 1.3	< 0.0001	4.6 ± 0.7	< 0.0001	NS	NS
Peak	8.9 ± 2.6		9.8 ± 2.5		NS	
VO_2, ml/kg/min						
Rest	3.7 ± 0.6	< 0.0001	3.6 ± 0.4	< 0.0001	NS	0.03
Peak	16.4 ± 2.8		18.4 ± 2.3		0.04	
< 16.0, n (%)	23 (46)		0 (0)		0.006	
VE/VCO_2 ratio	29.5 ± 5.2		29.0 ± 3.2		NS	
RER ratio at peak	1.17 ± 0.12		1.28 ± 0.10		0.008	
Systolic blood pressure, mmHg						
Rest	127 ± 21	< 0.0001	113 ± 17	< 0.0001	NS	NS
Peak	176 ± 31		176 ± 24		NS	
Diastolic blood pressure, mmHg						
Rest	67 ± 15	0.006	65 ± 14	NS	NS	NS
Peak	73 ± 14		71 ± 18		NS	
Heart rate, bpm						
Rest	66 ± 10	< 0.0001	70 ± 13	< 0.0001	NS	NS
Peak	118 ± 18		124 ± 18		NS	
%MHR at peak	77.8 ± 10.8		81.4 ± 11.4		NS	
Rate pressure product, mmHg x bpm						
Rest	8,334 ± 1,893	< 0.0001	7,978 ± 1,858	< 0.0001	NS	NS
Peak	20,789 ± 5,211		22,039 ± 5,809		NS	
Ea, mmHg/ml						
Rest	1.9 ± 0.6	< 0.0001	1.6 ± 0.4	0.01	NS	NS
Peak	2.3 ± 0.7		2.1 ± 0.6		NS	

VO_2, oxygen consumption; VE/VCO_2 ratio, ventilation to carbon dioxide output ratio; RER ratio, respiratory exchange ratio. MHR, maximum heart rate; Ea, effective arterial elastance.

Table 4. Univariate (R) of correlations between peak VO_2 and the different variables in patients with HFpEF.

Relation to Peak VO_2	HFpEF (n = 50)	
	Univariate correlation	
	R	P value
Age, years	-0.25	0.08
Sex	0.07	0.63
Hemoglobin, g/dl	0.22	0.12
Creatinine, mg/dl	0.05	0.75
Log NT-proBNP	-0.41	0.004
LAVI, ml/m^2	-0.23	0.11
LVEF, %	0.03	0.85
LVMI, g/m^2	-0.02	0.87
PA acceleration time, ms	0.15	0.32
E wave at rest, cm/s	-0.09	0.53
E wave at peak, cm/s	-0.004	0.98
A wave at rest, cm/s	0.04	0.78
A wave at peak, cm/s	0.25	0.11
E/A at rest	-0.20	0.18
E/A at peak	-0.24	0.14
S' at rest, cm/s	0.40	0.004
S' at peak, cm/s	0.46	0.0009
E' rest, cm/s	0.18	0.21
E' peak, cm/s	0.21	0.17
PASP at rest, mmHg	-0.05	0.74
PASP at peak, mmHg	-0.003	0.99
E/E' at rest	-0.31	0.03
E/E' at peak	-0.14	0.33
LVOT-VTI at rest, cm	0.22	0.13
LVOT-VTI at peak, cm	0.26	0.06
Stroke volume at rest, ml	0.29	0.04
Stroke volume at peak, ml	0.27	0.06
Cardiac output at rest, l/min	0.23	0.10
Cardiac output at peak, l/min	0.39	0.01
Systolic blood pressure at rest, mmHg	-0.05	0.70
Systolic blood pressure at peak, mmHg	0.17	0.23
Diastolic blood pressure at rest, mmHg	0.21	0.14
Diastolic blood pressure at peak, mmHg	0.24	0.10
Heart rate at rest, bpm	-0.19	0.19
Heart rate at peak, bpm	0.27	0.06
Ea at rest, mmHg/ml	-0.32	0.02
Ea at peak, mmHg/ml	-0.19	0.20

Table5. Multivariate (β) of correlations between peak VO_2 and the different variables in patients with HFpEF.

Relation to Peak VO_2	HFpEF (n = 50)			
	Multivariate regression		Multivariate regression	
	β (95% CI)	P value	β (95%CI)	P value
Age, years	-0.05 (-0.13 to 0.04)	0.27	-0.06 (-0.14 to 0.02)	0.15
Sex	-0.60 (-2.18 to 0.98)	0.45	-0.21 (-1.78 to 1.37)	0.79
Log NT-proBNP	-0.32 (-0.94 to 0.30)	0.30	-0.39 (-1.03 to 0.26)	0.23
S' at rest, cm/s			0.56 (-0.20 to 1.31)	0.14
S' at peak, cm/s	0.62 (0.02 to 1.22)	0.04		
E/E' at rest	-0.27 (-0.52 to -0.02)	0.04	-0.24 (-0.50 to 0.02)	0.07
Ea at rest, mmHg/ml	-0.23 (-1.45 to 1.00)	0.71	-0.31 (-1.59 to 0.97)	0.63

β, beta regression coefficient; CI, confidence interval.