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Suzuki, Makiko ; Sumimoto, Keiko ; Tanaka, Yusuke ; Yamashita, Kentaro...

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“Accelerated aging” of the heart as heart failure with preserved ejection fraction

～Analysis using leg-positive pressure stress echocardiography

Ayu Shono¹, MD; Kensuke Matsumoto^{1*}, MD, PhD; Nao Yamada², MD; Kenya Kusunose², MD, PhD; Makiko Suzuki¹, MD; Keiko Sumimoto¹, MD; Yusuke Tanaka¹, MD; Kentaro Yamashita,¹ MD; Nao Shibata¹, MD; Shun Yokota¹, MD, PhD; Makiko Suto¹, MD, PhD; Kumiko Dokuni¹, MD; Hidekazu Tanaka¹, MD, PhD; Ken-ichi Hirata¹, MD, PhD.

1) Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

2) Division of Cardiovascular Medicine, Department of Internal Medicine, Tokushima University Graduate School of Medicine, Tokushima, Japan

***Corresponding author**

Kensuke Matsumoto, MD, PhD

Division of Cardiovascular Medicine, Department of Internal Medicine

Kobe University Graduate School of Medicine

Address: 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan

TEL: +81-78-382-5846, FAX: +81-78-382-5859

E-mail: kenmatsu@med.kobe-u.ac.jp

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Abstract

Purposes: The aging process is a significant risk factor for heart failure. The incidence of heart failure with preserved ejection fraction (HFpEF) dramatically increases with age. Although HFpEF occurs along a continuum of aging of the cardiovascular system, the pathophysiology that differentiates overt HFpEF from physiological aging is not fully understood.

Methods: A total of 102 subjects were prospectively recruited: 25 patients with HFpEF and 77 healthy controls. Controls were stratified into three age-groups: young (n=27, 20-40 years), middle aged (n=25, 40-65 years), and elderly (n=25, >65 years). All participants underwent preload stress echocardiography using a leg-positive pressure (LPP) maneuver.

Results: With an increase in age, progressive concentric left ventricular (LV) remodeling was observed in healthy controls, resulting in the hemodynamic consequences of an age-dependent increase in the E/e' ratio (ANOVA, $P<0.001$). During LPP stress, the E/e' ratio significantly increased in the middle-aged and elderly groups (from 8 ± 2 to 9 ± 3 , from 10 ± 2 to 12 ± 3 , $P<0.05$, respectively), and this was more pronounced in patients with HFpEF (from 16 ± 5 to 17 ± 7 , $P<0.05$). Forward stroke volume (SV) significantly increased in each healthy group during LPP stress (all

$P<0.001$) but failed to increase in the HFpEF group (from 43 ± 13 to 44 ± 14 mL/m², $P=0.65$). In a multivariate analysis, LV mass index (odds ratio [OR] 1.051, $P<0.05$), E/e' ratio (OR 1.480; $P<0.05$), and change in SV (OR 0.780; $P<0.05$) were independent parameters that differentiated HFpEF from physiological aging.

Conclusions: Structural remodeling and impaired preload reserve **may** both be critical features that characterize the pathophysiology of HFpEF.

Keywords: Leg-positive pressure stress, Preload reserve, Heart failure with preserved ejection fraction, Aging

1 **Introduction**

2 As the aging population increases in number, so does the number of patients
3 with heart failure; this has become a significant medical, economic, and social problem.
4 In developed countries, heart failure occurs in 1%-2% of the adult population. The
5 number increases up to >10% among people aged >70.¹ Aging is associated with the
6 alteration of size,² number,³ and functions⁴ of the cardiomyocytes and the amount of
7 extracellular components,⁵ all of which contribute to an increase in myocardial stiffness
8 and diastolic dysfunction.⁶ Thus, aging is considered a significant risk factor for heart
9 failure.⁷ However, not all older people have, or will develop, clinical heart failure with
10 preserved ejection fraction (HFpEF). Overt HFpEF may result from multiple
11 abnormalities in the cardiovascular and other organ systems.⁸ However, the underlying
12 pathophysiology that differentiates physiological aging from overt HFpEF is not fully
13 understood.

14 Recently, a novel preload stress echocardiography using the leg-positive
15 pressure (LPP) maneuver was postulated to noninvasively reproduce a volume central
16 shift without any increase in the total body fluid volume. This maneuver can reveal the
17 preload reserve of patients with heart failure.⁹⁻¹¹ The essential feature of preload reserve
18 is the ability to enhance cardiac output without a significant increase in ventricular

filling pressure in response to increased venous return. Thus, the preload reserve can be regarded as representing the integrated function of both the contractile reserve and diastolic reserve.

This study aimed to assess the effects of the physiological aging process on cardiac structures and hemodynamics and to evaluate the determining factor that differentiates physiological aging from overt HFpEF by using a non-invasive preload increasing maneuver.

Methods

Study populations

For this study, a total of 102 subjects, including 25 patients with HFpEF and 77 healthy controls, were prospectively recruited from Kobe University Hospital and Tokushima University Hospital, Japan. Patients with HFpEF were defined as having a clear history of heart failure with typical symptoms that were accompanied by signs, including pulmonary congestion by chest radiography, biomarker elevation, confirmatory evidence of elevation in pulmonary capillary wedge pressure or left ventricular (LV) end-diastolic pressure by cardiac catheter examination, and an ejection fraction (EF) >50% at the time of enrolment.¹ All participants underwent transthoracic

1 echocardiography for the evaluation of hemodynamic status between April 2019 and
2 May 2020. The exclusion criteria were as follows: (1) uncontrolled blood pressure, (2)
3 current or prior severe disorders of other organs, (3) unstable heart failure with New
4 York Heart Association functional class IV, (4) pregnancy, (5) history of venous
5 thrombosis or pulmonary thromboembolism, (7) active skin lesions in the lower limbs,
6 and (8) more than moderate valvular heart disease. Upon enrolment, all patients were in
7 a clinically stable condition and received optimal pharmacological therapy. Control
8 participants were healthy volunteers recruited from the community and were screened
9 and excluded if they had any chronic medical illness, current medical complaints, or an
10 abnormal physical examination finding. After these evaluations, 77 healthy controls
11 were enrolled and stratified into three different age groups: young (n=27, 20-40 years),
12 middle-aged (n=25, 40-65 years), and elderly (n=25, >65 years). The H₂FPEF score was
13 calculated for all participants. The variables that comprise H₂FPEF score are obesity,
14 atrial fibrillation, age >60 years, treatment with two or more antihypertensives, E/e'
15 ratio >9, and echocardiographic pulmonary artery systolic pressure >35 mmHg.¹²

16 The protocol was registered with the University Hospital Medical Information
17 Network Clinical Trial Registry (UMIN 000033091). This study was approved by the
18 local ethics committee of our institution (protocol ID: 180134), and written informed

consent was obtained from all participants.

Echocardiographic examination

All echocardiographic studies were performed using commercially available echocardiography systems. Digital routine grayscale cine loops from three consecutive beats were obtained from LV parasternal and apical views. Echocardiographic measurements were obtained following the current guidelines of the European Association of Cardiovascular Imaging/ American Society of Echocardiography.¹³ LV volumes, EF, and left atrial (LA) volumes were calculated using the modified biplane Simpson's method, and all volumes and LV mass measurements were then normalized to the body surface area. For the assessment of LV remodeling, relative wall thickness (RWT) was measured as two times the posterior wall thickness divided by LV end-diastolic diameter, and the LV mass-to-volume ratio was calculated as the LV mass divided by the LV end-diastolic volume. The transmitral early diastolic (E) and atrial wave (A) velocities were measured using pulsed-wave Doppler recordings from the apical four-chamber view.¹⁴ Early diastolic (e') mitral annular velocity was measured using spectral tissue Doppler imaging with a sample volume placed at the septal and lateral mitral annulus, and the averaged value of the E/e' ratio was calculated to estimate the LV filling pressure.¹⁴ Forward stroke volume (SV) was determined in terms

of the velocity-time integral, assessed using pulsed-wave Doppler positioned at the LV outflow tract. The right ventricular (RV) fractional area change was measured using the RV-focused four-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was measured as an index of longitudinal RV systolic function.¹³

Preload stress echocardiography

For the preload stress test, commercially available LPP equipment (Dr Medomer DM-5000EX, Medo Industries Co, Ltd, Tokyo, Japan) was used. The procedure of the LPP stress maneuver has been described in detail.⁹⁻¹¹ In brief, it was designed to provide a continuous external pressure around the lower limbs using dedicated airbags at 90 mmHg (Figure 1, right upper panel and Movie clip). This pressure was proven to safely provide an increase in ventricular preload based on the findings from the invasive hemodynamic study.¹¹ Echocardiographic measurements were obtained both at rest and during LPP stress. All LPP stress echocardiographic examinations were performed 20 s after inflation of the airbags. Electrocardiogram, blood pressure, and heart rate were monitored during the entire procedure.

Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data and as the median and interquartile range for non-normally

distributed data. Categorical variables were expressed as frequencies and percentages. Differences in baseline echocardiographic and hemodynamic parameters between subgroups were tested by one-way analysis of variance (ANOVA), followed by posthoc comparisons by Tukey test. The paired *t* test was used to compare differences in hemodynamic and echocardiographic parameters between the two time points. The initial univariate logistic regression analysis to identify univariate factors for identifying HFpEF was followed by a multivariate analysis using a stepwise selection, with the *P* levels for entry into the model set at <0.10. Nested logistic regression models were then constructed to determine the incremental diagnostic value of the preload reserve during LPP stress over H₂FPEF score and LV mass index. A significant increase in the global log-likelihood χ^2 value of the model defined incremental prognostic value. Receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-off points of echocardiographic parameters as well as to calculate the area under the curve (AUC) for each of the indexes for differentiating patients with HFpEF from age-matched individuals without heart failure symptoms. All tests were two tailed, with differences reported as significant if *P*<0.05. All analyses were performed with MedCalc version 19.4.1 (MedCalc Software; Ostend, Belgium).

Results

Baseline characteristics

A summary of the baseline clinical characteristics of the 25 patients with HFpEF is presented in Table 1. As shown in the table, patients with HFpEF were predominantly older women with NYHA functional class II-III symptoms of exertional dyspnea. In this cohort, most patients with HFpEF were not obese, half had hypertension, and a third had diabetes mellitus. Blood pressure was well controlled by antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β -blockers, and spironolactone.

Table 2 shows the comparisons of baseline clinical, hemodynamic, and echocardiographic characteristics of patients with HFpEF and healthy controls from the three age groups. Regarding the structural parameters, the LV mass index progressively increased with physiological aging. Conversely, the LV end-diastolic volume showed a progressive decrease with aging. As a result of these morphological alterations, age-dependent progressive concentric LV remodeling was confirmed, as evidenced by the significant increase in RWT and LV mass-to-volume ratio, which was further pronounced in patients with HFpEF. By contrast, parameters of resting LV and RV systolic function including LVEF, TAPSE, and RV fractional area change were

consistently preserved regardless of aging. Regarding the diastolic function, e' velocity progressively decreased, and the E/e' ratio significantly increased with aging, indicating an age-dependent reduction in ventricular relaxation property and elevated ventricular filling pressure (ANOVA, $P<0.001$, respectively). The E/e' ratio further elevated in patients with HFpEF ($P<0.05$ vs each control subgroup). As a result, LAVI showed an age-dependent progressive increase in healthy controls, which was further increased in patients with HFpEF ($P<0.05$ vs each control subgroup).

Preload stress test

The acute preload stress test was well tolerated by all participants without any complications associated with the LPP maneuver. Table 3 shows the comparisons of the response to LPP stress for each healthy control subgroup and patients with HFpEF. As a result of LPP stress, LV volumes, E-wave velocity, and LA volume significantly increased in each group soon after the LPP maneuver, indicating that LPP stress could offer sufficient preload augmentation for these subjects. Intriguingly, LPP stress resulted in a significant increase in forward SV without any elevation in the LV filling pressure in the young subgroup (Figure 1). By contrast, forward SV significantly increased at the expense of an elevation in the LV filling pressure in both the middle-aged and elderly subgroups during LPP stress (Figure 1). The Frank-Starling

mechanism was significantly impaired (SVi: from 43 ± 13 to 44 ± 14 mL/m², $P=0.65$), and the E/e' ratio was seriously elevated (from 15.0 ± 5.3 to 17.4 ± 7.4 , $P<0.05$) in patients with HFpEF in response to the acute preload-increasing intervention (Figure 1).

Structural and hemodynamic characteristics that discriminate the pathophysiology of HFpEF

The odds ratios (OR) and 95% confidence intervals (CI) for each variable in the univariate and multivariate analyses for identifying HFpEF are shown in Table 4. In a multivariate logistic regression analysis, LV mass index (OR 1.051 per 10 g/m² increase, $P<0.05$), baseline E/e' ratio (OR 1.480 per 5 unit increase, $P<0.05$), and Δ SVi (OR 0.780 per 5 mL/m² increase, $P<0.05$) during LPP stress were the independent determining characteristics of overt HFpEF.

In the nested logistic regression models, a model based on the H₂FPEF score (model 1: $\chi^2=31.7$) was improved by the addition of LV mass index (model 2: $\chi^2=48.1$, $P<0.001$). The model was further improved by the addition of Δ SVi during LPP stress (model 3: $\chi^2=54.3$, $P<0.05$).

For differentiating patients with HFpEF from elderly subgroup without HF, ROC curve analysis identified the optimal cut-off value of the LV mass index as 94.6 g/m² (sensitivity, 64.0%; specificity, 92.2%; AUC, 0.854; $P<0.001$), baseline E/e' ratio

as 11.4 (sensitivity, 72.0%; specificity, 89.6%; AUC, 0.893; $P<0.001$), and ΔSV_i as 0.4 mL/m² (sensitivity, 56.0%; specificity, 96.1%; AUC, 0.728; $P<0.01$).

Figure 2 shows representative cases of patients with HFpEF and healthy controls from the three age groups.

Discussion

This study has several significant findings. First, age-dependent progressive concentric LV remodeling was observed as a physiological aging process. Along with these morphological alterations, the ventricular relaxation property and LV filling pressure progressively deteriorated. Second, these structural and functional signs of the “aging of the heart” were further accelerated in HFpEF (“accelerated aging”). Finally, the HFpEF group had significantly impaired preload reserve, which is an important hemodynamic feature that characterized the pathophysiology of HFpEF. Moreover, the lack of preload reserve showed incremental diagnostic value over LV hypertrophy and the existing diagnostic scoring system.

Age-dependent alterations in cardiac structure and function

Aging is associated with numerous changes in the human heart at the molecular, cellular, and chamber levels.^{3, 5, 15-17} Alterations in organ morphology are

1 closely paralleled with differences at the microscopic level; thus, despite the progressive
2 cardiomyocyte dropout with aging,³ hypertrophy of the individual cardiomyocytes and
3 the increased extracellular matrix leads to the net results of preserved LV mass as
4 observed in this study. A previous study using cardiac magnetic resonance imaging
5 clearly showed marked age-dependent progressive decline in LV volume of 0.8-0.9 mL
6 per year.¹⁷ The authors also demonstrated the significant age-dependent increase in the
7 mass-to-volume ratio, which was mainly driven by a disproportionate shrinkage in
8 ventricular size in comparison with the ventricular mass volume. In this way, age-
9 dependent cardiomyocyte dropout, increased collagen deposition, mitochondrial
10 dysfunction and impairment of calcium signaling, and concentric ventricular
11 remodeling can all contribute to the impaired contractility and abnormal diastolic
12 property.^{3, 5, 15, 17}

13 The structural and hemodynamic hallmarks of HFpEF are concentric
14 hypertrophy accompanied by diastolic abnormalities, including delayed relaxation,
15 myocardial stiffening, and associated impairment of filling dynamics. Therefore, the
16 process of both structural and functional changes in a HFpEF heart can be considered
17 fundamentally the same as that of a senescent heart,¹⁸ which may be further accelerated
18 by various comorbidities such as hypertension, diabetes mellitus, or chronic kidney

disease.¹⁹

Altered response in hemodynamic stress

In addition to the structural and functional changes, one of the most important hemodynamic aspects that characterize the senescent cardiovascular system is the impairment of followability to the dynamic fluctuations in hemodynamic states, which is further pronounced in patients with HFpEF. As regards the contractile reserve, Kitzman et al.²⁰ examined the exercise capacity of patients with HFpEF with invasive cardiopulmonary exercise testing. They showed that patients with HFpEF demonstrated severe exercise intolerance with a 48% reduction in peak oxygen consumption, mainly due to a 41% reduction in peak cardiac output, when compared with normal subjects.

Interestingly, in patients with HFpEF, an increased response in both peak LV end-diastolic volume and peak SV was significantly blunted compared with those of normal subjects, which indicates that the preload reserve and contractile reserve were significantly impaired in patients with HFpEF. By contrast, Fujimoto et al.²¹ examined a total of 71 normal subjects and patients with HFpEF who received volume challenge with rapid saline infusion and found that patients with HFpEF exhibited a steeper increase in pulmonary capillary wedge pressure relative to the infused volume than healthy young and older subjects. Although they speculated that the latent impairment

of diastolic and systolic dysfunction might be responsible for the impaired response to the hemodynamic load, characteristic concentric LV remodeling itself in elderly individuals and in patients with HFpEF may be attributable to the lack of preload reserve. From a physiological point of view, cardiac preload is wall stress (σ) at end-diastole; thus, cardiac preload can be presented as the following formula by using Laplace's law:

$$\sigma_{\text{end-diastole}} \supseteq r_{\text{end-diastole}} \times P_{\text{end-diastole}} / 2h_{\text{end-diastole}}$$

where r is the chamber radius, P is the intra-ventricular pressure, and h is the wall thickness.

On the other hand, RWT is given as the following formula.

$$\text{RWT} = 2h_{\text{end-diastole}} / 2r_{\text{end-diastole}}$$

Based on these two formulae, LV end-diastolic pressure can be transformed into

$$P_{\text{end-diastole}} \supseteq \sigma_{\text{end-diastole}} \times 2\text{RWT}$$

This formula can explain the significant hemodynamic instability observed in the elderly individuals and in patients with HFpEF, in which even a small increase in ventricular preload ($\sigma_{\text{end-diastole}}$) will result in a marked elevation in the LV end-diastolic pressure ($P_{\text{end-diastole}}$) as a consequence of a greater RWT. In other words, concentric remodeling itself can be considered ultimately vulnerable to the increased preload.

Vascular stiffening associated with HFpEF produces greater blood pressure lability with changes in various hemodynamic stressors.²² If ventricular afterload abruptly increased, the decreased cardiac output is usually compensated by recruiting preload reserve. As a result, patients with concentric remodeling **may** easily develop significant elevation in LV end-diastolic pressure, subsequent LA and pulmonary venous hypertension, and eventually decompensated heart failure.

From a hemodynamic point of view, the cardiac output must always be kept in balance with an LV input. However, in senescent and diseased hearts, the increased output cannot be accomplished by the impaired preload reserve. The Guyton diagram can explain these pathophysiological mechanisms (Figure 3). At any given hemodynamic state, the intersection point of the two curves of the cardiac preload and output identifies the ventricular filling pressure. During LPP stress, the venous return curve shifts toward the right. At the same time, the intersection point shifts toward a new steady state at which venous return and cardiac output are equalized, which results in an increased cardiac output with minimal change in filling pressure in the young healthy subgroup (Figure 3). When the Frank-Starling curve shifts downward with physiological aging, the increased venous return will result in a small gain in the cardiac output, along with a significant increase in filling pressure, as observed in the middle-

aged and elderly subgroups (Figure 3). When the ventricular function is further impaired, as a result of a relatively flat Frank-Starling curve, the increased venous return **may** no longer contribute to the effective increase in cardiac output. Instead, the filling pressure **would** rise dramatically, as observed in our patients with HFpEF (Figure 3).

Clinical implications

Although some diagnostic scoring systems have been proposed,^{12, 19} the accurate diagnosis of HFpEF is still challenging, because symptoms may be related to deconditioning, obesity, lung disease, pulmonary vascular disease, or HFpEF. Exercise stress testing may be performed to confirm the elevated filling pressure during exercise when parameters obtained at rest are unremarkable.^{14, 20, 23} HFpEF is, however, mostly a disease of the elderly, and maximal exercise is often not feasible for these patients. By contrast, LPP stress can permit us to investigate patients who are elderly with insufficient exercise capacity and those with orthopedic problems. Moreover, LPP stress echocardiography is safe, cost-effective, not time-consuming, and easy to perform.⁹

Therefore, we believe this novel technique may potentially be complementary to cardiopulmonary exercise test or useful when exercise stress is submaximal. The findings of LPP stress echocardiography may lead to crucial clinical decision-making

and clinical management, especially for patients with unexplained dyspnea. Moreover, a practical implication of our results is that preload stress echocardiography using LPP could identify patients at potentially high risk and likely to develop clinical deterioration before they manifest hemodynamic decompensation.

Limitations

This study has certain limitations. First, results from speckle-tracking strain analysis or other imaging techniques such as cardiac magnetic resonance imaging were not included in this study. Reddy et al.²⁴ elegantly reported that LA reservoir strain provided enhanced diagnostic accuracy beyond conventional echocardiographic measures to discriminate HFpEF from non-cardiac cause of dyspnea by using speckle-tracking echocardiography. On the other hand, Backhouse et al.²⁵ clearly showed that real-time cardiac magnetic resonance imaging allowed highly accurate identification of HFpEF during physiological exercise and qualified as a suitable non-invasive diagnostic alternative. However, one of the most important aspects of this study is its simplicity without using complicated techniques. Practically, hemodynamic assessment using LPP stress echocardiography will be valuable because it is not time-consuming and easy to perform in daily clinical settings. Second, although this was a prospective multicenter study, this pilot study covered a relatively small number of patients with HFpEF and

should be considered a hypothesis-generating investigation; thus, further studies with a larger patient population will be needed to validate our findings. Third, the measurements of the echocardiographic parameters did not include blinding process. However, because two experienced echocardiographers performed structural and hemodynamic assessments without prejudice, we believe that the results of our study would be clinically relevant. Moreover, because the clinical background of HFpEF and control subjects from three age groups are not homogeneous, results of comparisons of echocardiographic parameters should be interpreted carefully. Fourth, LV volumes of the study participants appear small. Volumetric assessment using bi-plane two-dimensional Simpson's method is known to consistently underestimate LV volumes compared with those obtained by three-dimensional echocardiography and cardiac magnetic resonance imaging,²⁶ because two-dimensional measurements were based on various geometric assumptions, which introduce significant errors. In this study, however, forward SV was not calculated by LV volumes but assessed by Doppler method. Therefore, we believe the major findings of our study would be clinically relevant. Finally, e' velocity was measured only from the apical four-chamber view as the averaged value in this study, and it is well known that the E/e' ratio can be affected by significant mitral annular calcification or mitral regurgitation. However, patients

with more than moderate valvular diseases and those with significant mitral annular calcification were not included in this study; therefore, we believe that the methodology of the measurement of the E/e' ratio may not influence the overall results of this study.

Conclusions

Striking parallels between structure-function differences between the aging heart and HFpEF heart were observed in the physiological cardiac aging process, which was further accelerated in HFpEF. Both structural remodeling and impaired preload reserves may be important hemodynamic features that characterize the pathophysiology of HFpEF.

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Conflict of interest: The authors declare no conflicts of interest.

1 **References**

- 2 1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V,
3 Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C,
4 Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope
5 LM, Ruschitzka F, Rutten FH, van der Meer P and Group ESCSD. 2016 ESC
6 Guidelines for the diagnosis and treatment of acute and chronic heart failure:
7 The Task Force for the diagnosis and treatment of acute and chronic heart
8 failure of the European Society of Cardiology (ESC) Developed with the
9 special contribution of the Heart Failure Association (HFA) of the ESC. *Eur*
10 *Heart J.* 2016;37:2129-2200.
- 11 2. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J,
12 Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and
13 function differ in systolic and diastolic heart failure. *Circulation.*
14 2006;113:1966-1973.
- 15 3. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging
16 human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res.*
17 1991;68:1560-1568.
- 18 4. Babusikova E, Lehotsky J, Dobrota D, Racay P, Kaplan P. Age-associated

- 1 changes in Ca(2+)-ATPase and oxidative damage in sarcoplasmic reticulum of
- 2 rat heart. *Physiol Res*. 2012;61:453-460.
- 3 5. Gazoti Debessa CR, Mesiano Maifrino LB, Rodrigues de Souza R. Age related
- 4 changes of the collagen network of the human heart. *Mech Ageing Dev*.
- 5 2001;122:1049-1058.
- 6 6. Katz AM, Rolett EL. Heart failure: when form fails to follow function. *Eur*
- 7 *Heart J*. 2016;37:449-454.
- 8 7. Lakatta EG, Sollott SJ. Perspectives on mammalian cardiovascular aging:
- 9 humans to molecules. *Comp Biochem Physiol A Mol Integr Physiol*.
- 10 2002;132:699-721.
- 11 8. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA,
- 12 Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved
- 13 Ejection Fraction: A Multiorgan Roadmap. *Circulation*. 2016;134:73-90.
- 14 9. Matsumoto K, Onishi A, Yamada H, Kusunose K, Suto M, Hatani Y, Matsuzoe
- 15 H, Tatsumi K, Tanaka H, Hirata KI. Noninvasive Assessment of Preload
- 16 Reserve Enhances Risk Stratification of Patients With Heart Failure With
- 17 Reduced Ejection Fraction. *Circ Cardiovasc Imaging*. 2018;11:e007160.
- 18 10. Yamada H, Kusunose K, Nishio S, Bando M, Hotchi J, Hayashi S, Ise T, Yagi

- 1 S, Yamaguchi K, Iwase T, Soeki T, Wakatsuki T, Sata M. Pre-load stress
2 echocardiography for predicting the prognosis in mild heart failure. *JACC*
3 *Cardiovasc Imaging*. 2014;7:641-649.
- 4 11. Kusunose K, Yamada H, Nishio S, Tamai R, Niki T, Yamaguchi K, Taketani Y,
5 Iwase T, Soeki T, Wakatsuki T, Sata M. Interval from the onset of transmitral
6 flow to annular velocity is a marker of LV filling pressure. *JACC Cardiovasc*
7 *Imaging*. 2013;6:528-530.
- 8 12. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple,
9 Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With
10 Preserved Ejection Fraction. *Circulation*. 2018;138:861-870.
- 11 13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L,
12 Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru
13 D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU.
14 Recommendations for cardiac chamber quantification by echocardiography in
15 adults: an update from the American Society of Echocardiography and the
16 European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*.
17 2015;28:1-39 e14.
- 18 14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen

- 1 T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK,
2 Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left
3 Ventricular Diastolic Function by Echocardiography: An Update from the
4 American Society of Echocardiography and the European Association of
5 Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.
- 6 15. Tocchi A, Quarles EK, Basisty N, Gitari L, Rabinovitch PS. Mitochondrial
7 dysfunction in cardiac aging. *Biochim Biophys Acta*. 2015;1847:1424-33.
- 8 16. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR,
9 Anversa P. Gender differences and aging: effects on the human heart. *J Am Coll*
10 *Cardiol*. 1995;26:1068-1079.
- 11 17. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima
12 JA. Age-related left ventricular remodeling and associated risk for
13 cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circ*
14 *Cardiovasc Imaging*. 2009;2:191-198.
- 15 18. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. *Physiol*
16 *Rev*. 1993;73:413-467.
- 17 19. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann
18 F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel

- 1 E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors
2 AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart
3 failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a
4 consensus recommendation from the Heart Failure Association (HFA) of the
5 European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297-3317.
- 6 20. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise
7 intolerance in patients with heart failure and preserved left ventricular systolic
8 function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol*.
9 1991;17:1065-1072.
- 10 21. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS,
11 Carrick-Ranson G, Levine BD. Hemodynamic responses to rapid saline
12 loading: the impact of age, sex, and heart failure. *Circulation*. 2013;127:55-62.
- 13 22. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart*
14 *Fail Clin*. 2008;4:23-36.
- 15 23. Rommel KP, von Roeder M, Oberueck C, Latuscynski K, Besler C, Blazek S,
16 Stiermaier T, Fengler K, Adams V, Sandri M, Linke A, Schuler G, Thiele H,
17 Lurz P. Load-Independent Systolic and Diastolic Right Ventricular Function in
18 Heart Failure With Preserved Ejection Fraction as Assessed by Resting and

1 Handgrip Exercise Pressure-Volume Loops. *Circ Heart Fail*. 2018;11:e004121.

2 24. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug
3 BA. Left atrial strain and compliance in the diagnostic evaluation of heart
4 failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21:891-900.

5 25. Backhaus SJ, Lange T, George EF, Hellenkamp K, Gertz RJ, Billing M,
6 Wachter R, Steinmetz M, Kutty S, Raaz U, Lotz J, Friede T, Uecker M,
7 Hasenfuss G, Seidler T, Schuster A. Exercise Stress Real-Time Cardiac
8 Magnetic Resonance Imaging for Noninvasive Characterization of Heart
9 Failure With Preserved Ejection Fraction: The HFpEF-Stress Trial. *Circulation*.
10 2021;143:1484-1498.

11 26. Caiani EG, Corsi C, Zamorano J, Sugeng L, MacEneaney P, Weinert L, Battani
12 R, Gutierrez-Chico JL, Koch R, Perez de Isla L, Mor-Avi V, Lang RM.
13 Improved semiautomated quantification of left ventricular volumes and
14 ejection fraction using 3-dimensional echocardiography with a full matrix-
15 array transducer: comparison with magnetic resonance imaging. *J Am Soc*
16 *Echocardiogr*. 2005;18:779-788.

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Figure legends

Figure 1. Stroke volume index and E/e' plot at baseline and during LPP stress for each age group and patients with HFpEF.

Each plot represents the mean values. The arrows indicate the changes in these parameters from those obtained under resting conditions to those obtained during leg-positive pressure (LPP) stress.

LPP = leg-positive pressure, HFpEF = heart failure with preserved ejection fraction, SVi = stroke volume index.

Figure 2. Representative cases of each age-group and a patient with HFpEF.

For a healthy young subject (upper left), the stroke volume index (SVi) increased in response to leg-positive pressure (LPP) stress, while the E/e' ratio remained unchanged.

For middle-aged and elderly subjects (upper right and lower left), SVi increased during LPP stress at the expense of the increase in E/e'. For a patient with HFpEF, SVi failed to increase during LPP stress. The E/e' ratio dramatically increased in response to LPP stress.

LPP = leg-positive pressure, LVOT = left ventricular outflow, TMF = transmitral flow,

TDI = tissue Doppler imaging, SVi = stroke volume index, HFpEF = heart failure with

1 preserved ejection fraction.

2

3 **Figure 3. Schematic presentation of the hemodynamic responses on the Guyton**
4 **diagram for each subgroup during acute preload-increasing maneuver.**

5 The difference in hemodynamic responses to the increased preload according to age
6 groupss and HFpEF are schematically presented in the Guyton diagram.

7 LPP = leg-positive pressure, LV = left ventricular, HFpEF = heart failure with preserved
8 ejection fraction.

Figure 1

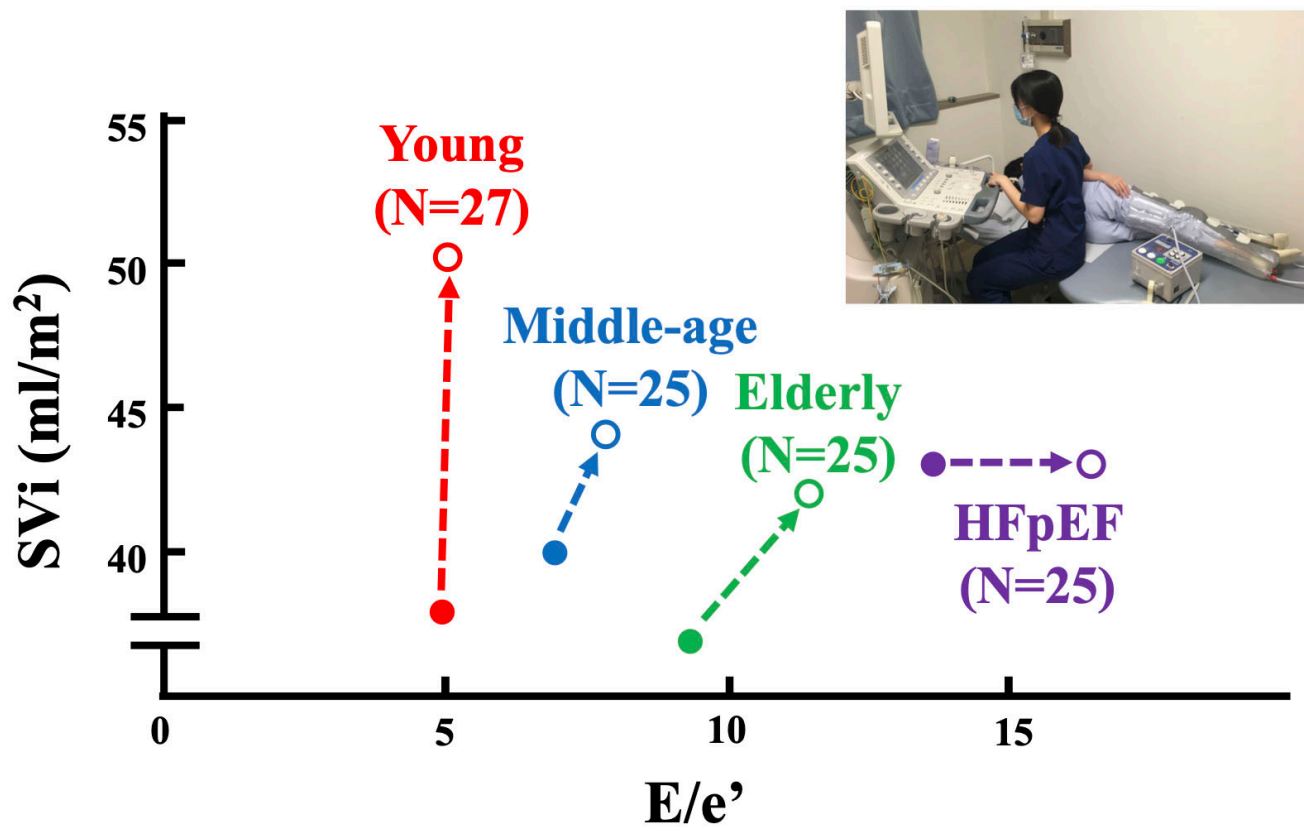


Figure 2

Young

Middle-age

Elderly

HFpEF

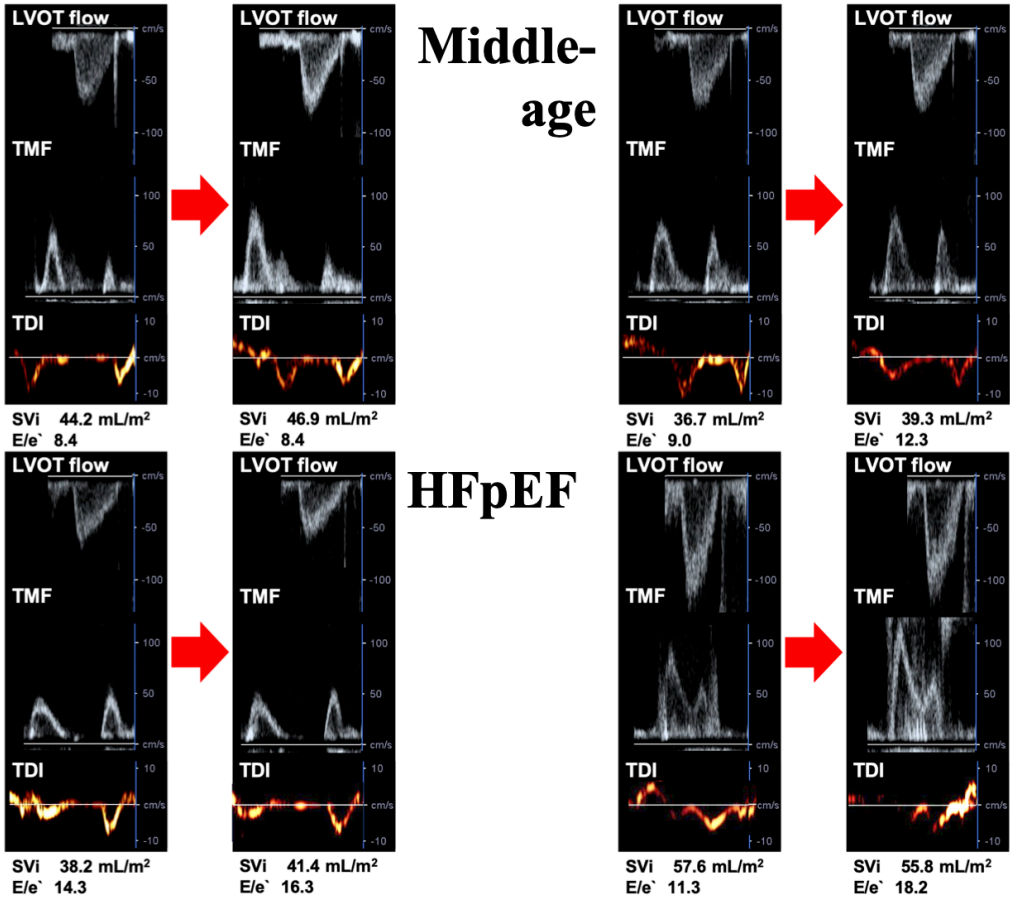


Figure 3

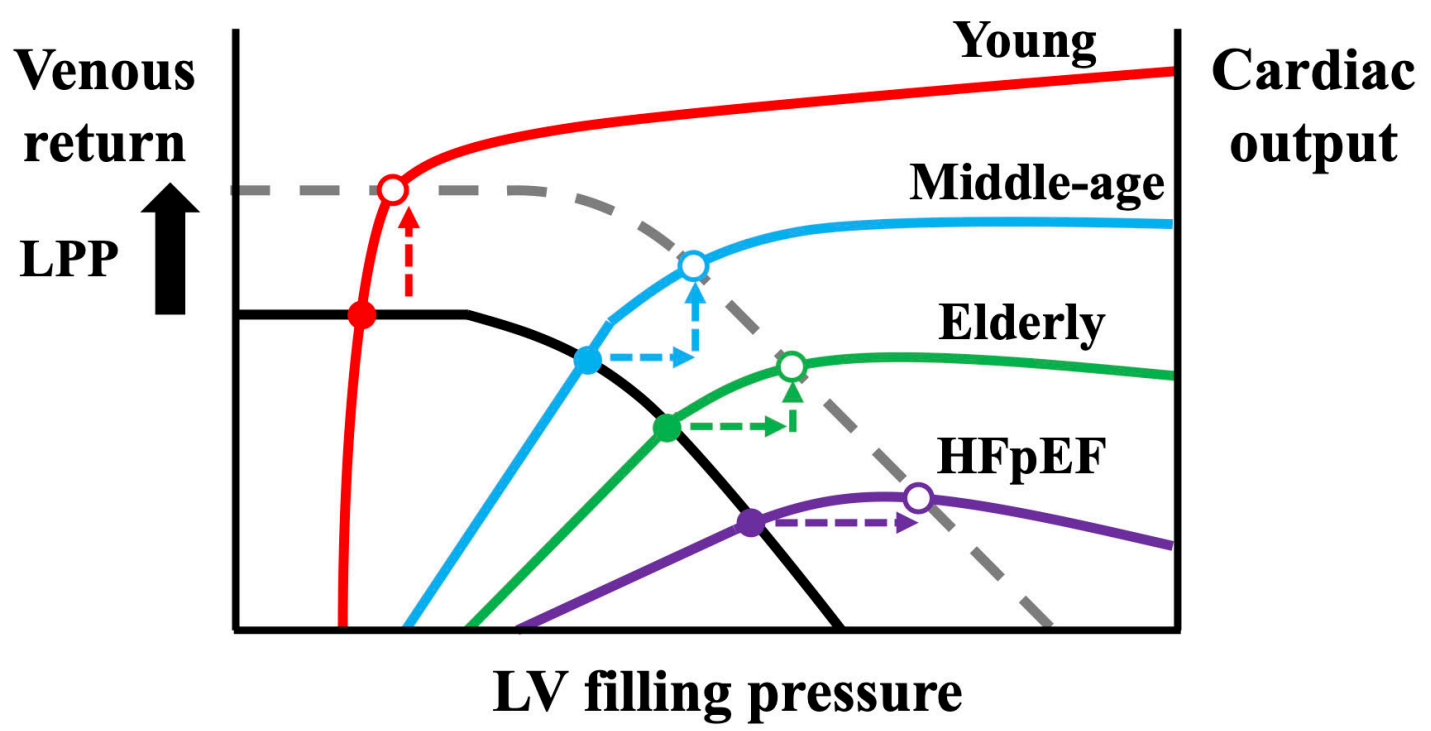


Table 1. Clinical characteristics of patients with HFpEF

Age, y	76 ± 13
Gender, M/F	10/15
BMI	23 ± 4
H ₂ FPEF score	2.6 ± 1.6
Comorbidities, n (%)	
Hypertension	14 (56)
Diabetes mellitus	9 (36)
Dyslipidemia	12 (48)
COPD	5 (20)
Cardiac rhythm	
Sinus rhythm, n (%)	23 (92)
Atrial fibrillation, n (%)	2 (8)
NYHA functional class, n (%)	
II	19 (76)
III	6 (24)
IV	0 (0)
Medications, n (%)	
Loop diuretics	14 (56)
Beta-blockers	14 (56)
Spironolactone	6 (24)
ACE-I/ARBs	14 (56)
Hemoglobin, g/dL	12.1 ± 2.1
B-type natriuretic peptide, pg/mL	158 (105-262)
eGFR, mL/min/1.73m ²	55.2 ± 20.6

Data are presented as n, mean ± SD, n (%), or median (interquartile range).

HFpEF, heart failure with preserved ejection fraction; COPD, chronic obstructive lung disease; NYHA, New York Heart Association; ARB, angiotensin II receptor blocker; ACE-I, angiotensin converting enzyme-inhibitor; eGFR, estimated glomerular filtration rate.

Table 2. Baseline characteristics for patients with HFpEF and normal controls from 3 age -groups

Variables	Young (N=27)	Middle-age (N=25)	Elderly (N=25)	HFpEF (N=25)	ANOVA <i>P</i> value
Age, y	23 ± 4	52 ± 6*	77 ± 6*†	76 ± 13*†	<0.001
Gender, M/F	13/14	6/19	12/13	10/15	0.14
Echocardiographic characteristics					
LV volume index, mL/m ²					
End-diastole	53 ± 10	42 ± 12*	39 ± 9*	43 ± 14*	<0.001
End-systole	19 ± 4	16 ± 5	14 ± 4*	17 ± 8	<0.05
LVOT-SVi, mL/m ²	38 ± 7	40 ± 6	37 ± 8	43 ± 13	0.11
LV mass index, g/m ²	69 ± 17	69 ± 18	81 ± 21	110 ± 31*†‡	<0.001
Mass to volume ratio, g/mL	1.3 ± 0.4	1.7 ± 0.5	2.2 ± 0.7*†	2.7 ± 0.9*†‡	<0.001
Relative wall thickness	0.33 ± 0.06	0.42 ± 0.09*	0.55 ± 0.10*†	0.58 ± 0.18*†	<0.001
LVEF, %	64 ± 3	63 ± 4	63 ± 5	61 ± 7	0.07
E/A ratio	2.2 ± 0.7	1.1 ± 0.3*	0.8 ± 0.2*†	1.3 ± 0.5*†‡	<0.001
LAVI, mL/m ²	19 ± 7	27 ± 5	31 ± 8*†	51 ± 18*†	<0.001
e' velocity, cm/sec	15 ± 2	10 ± 2*	6 ± 2*†	6 ± 2*†	<0.001
E/e' ratio	6 ± 2	8 ± 2	10 ± 2*†	15 ± 5*†‡	<0.001
RVFAC, %	34 ± 10	43 ± 7*	47 ± 10*	48 ± 11*	<0.01
TAPSE, mm	22 ± 4	24 ± 4	23 ± 5	22 ± 5	0.18

Data are presented as n, mean ± SD, n (%).

HFpEF, heart failure with preserved ejection fraction; SVi, stroke volume index; LV, left ventricular;

LVOT, left ventricular outflow tract; LA, left atrial; LAVI, left atrial volume index; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

* *P*<0.05 vs. young group, † *P*<0.05 vs. middle-aged group, ‡ *P*<0.05 vs elderly group

Table. 3 Changes in hemodynamic and echocardiographic parameters during leg-positive pressure stress for patients with HFpEF and normal controls from 3 age -groups

	Young (N=27)		Middle-aged (N=25)		Elderly (N=25)		HFpEF (N=25)	
	Baseline	LPP	Baseline	LPP	Baseline	LPP	Baseline	LPP
Hemodynamics								
Systolic BP, mmHg	119 ± 16	107 ± 14*	115 ± 17	112 ± 16	134 ± 22	125 ± 21*	129 ± 25	124 ± 23*
Diastolic BP, mmHg	69 ± 11	61 ± 11*	69 ± 10	69 ± 11	76 ± 15	74 ± 10	68 ± 13	70 ± 18
HR, bpm	69 ± 11	67 ± 10	70 ± 11	66 ± 10*	74 ± 15	69 ± 13*	71 ± 11	67 ± 12
SVi, mL/m ²	38 ± 7	42 ± 8*	40 ± 6	44 ± 6*	37 ± 8	42 ± 8*	43 ± 13	44 ± 14
Echocardiographic indices								
LV volume index, mL/m ²								
End-diastole	53 ± 10	55 ± 9	42 ± 12	49 ± 15*	39 ± 9	43 ± 7*	43 ± 14	47 ± 13*
End-systole	19 ± 4	20 ± 4*	16 ± 5	16 ± 6	14 ± 4	15 ± 3	17 ± 8	18 ± 9
LVEF, %	64 ± 3	64 ± 4	63 ± 4	68 ± 5*	63 ± 5	66 ± 4*	61 ± 7	63 ± 6
Transmitral flow parameters								
E velocity, cm/sec	81 ± 16	86 ± 14*	72 ± 18	75 ± 14	61 ± 13	67 ± 13*	84 ± 21	90 ± 23*
A velocity, cm/sec	39 ± 10	39 ± 10	65 ± 13	69 ± 14	83 ± 17	83 ± 15	72 ± 26	73 ± 27
E/A ratio	2.2 ± 0.7	2.3 ± 0.7	1.1 ± 0.3	1.1 ± 0.3	0.8 ± 0.2	0.8 ± 0.2*	1.3 ± 0.5	1.4 ± 0.7*
LAVI, mL/m ²	19 ± 7	21 ± 7*	27 ± 5	30 ± 6*	31 ± 8	35 ± 11*	51 ± 18	53 ± 18
e' velocity, cm/sec	15 ± 2	15 ± 2*	10 ± 2	9 ± 2	6 ± 2	6 ± 1*	6 ± 12	6 ± 2
E/e' ratio	6 ± 2	6 ± 1	8 ± 2	9 ± 3*	10 ± 2	12 ± 3*	15 ± 5	17 ± 7*
TR-PG, mmHg	16 ± 5	18 ± 4	15 ± 4	15 ± 5	20 ± 7	19 ± 6	23 ± 6	24 ± 9
RVFAC, %	34 ± 10	37 ± 10	43 ± 7	54 ± 6*	47 ± 10	54 ± 12*	48 ± 11	48 ± 9
TAPSE, mm	22 ± 4	23 ± 5*	24 ± 4	25 ± 4*	23 ± 5	26 ± 4*	22 ± 5	21 ± 6
IVC diameter, mm	16 ± 4	16 ± 4	13 ± 4	13 ± 3	13 ± 4	14 ± 4*	14 ± 5	15 ± 5

Data are presented as mean ± SD.

LPP, leg-positive pressure; BP, blood pressure; HR, heart rate; TR, tricuspid regurgitation; PG, pressure gradient; IVC, inferior vena cava. All other abbreviations as in Table 1 and 2. **P*<0.05 vs. baseline.

Table 4. Univariate and multivariate logistic regression analysis to identify HFpEF

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Clinical variables						
Age (per 5 years increase)	1.076	1.037-1.160	<0.001			
Gender (female)	0.957	0.381-2.407	0.93			
H ₂ FpEF score	2.968	1.828-4.817	<0.001			
Baseline echocardiographic variables						
SVi (per 5 mL/m ² increase)	1.059	1.007-1.113	0.03			
LVEDVI (per 5 mL/m ² increase)	0.986	0.949-1.024	0.47			
LV mass index (per 10 g/m ² increase)	1.063	1.036-1.109	<0.001	1.051	1.016-1.087	<0.01
RWT (per 0.05 unit increase)	1.069	1.032-1.108	<0.001			
LVEF (per 5% increase)	0.880	0.793-0.976	0.02			
LAVI (per 5 mL/m ² increase)	1.251	1.134-1.379	<0.001			
E/e' (per 5 unit increase)	1.473	1.240-1.750	<0.001	1.480	1.181-1.855	<0.001
TAPSE (per 5 mm increase)	0.941	0.846-1.045	0.26			
Variables during LPP stress						
Δ SVi (per 5 mL/m ² increase)	0.754	0.644-0.883	<0.001	0.780	0.646-0.941	<0.01
Δ E/e' (per 5 unit increase)	1.234	1.038-1.468	0.02			

OR, odds ratio; CI, confidence interval. All other abbreviations as in Table 1, 2 and 3.