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Contributions of Nondiastolic Factors to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Heart failure with preserved ejection fraction (HFpEF) has a complex etiology. Factors responsible for development of impaired exercise tolerance and disease progression are incompletely defined.

OBJECTIVES The authors sought to define the contributions of contractile reserve, ventriculo-arterial coupling (VAC) reserve, and chronotropic response to the progression of HFpEF.

METHODS We performed echocardiography at rest and immediately post-cardiopulmonary exercise test in 207 patients (63 ± 8 years of age) with stage C heart failure (HF) (exertional dyspnea, New York Heart Association functional class II to III, exercise capacity <80% of normal, left ventricular ejection fraction >50%, and diastolic dysfunction) and 60 patients with stage B HF (normal exercise tolerance with left ventricular hypertrophy, and/or reduced global longitudinal strain, with diastolic dysfunction).

RESULTS Symptomatic patients were grouped as stage C1 (ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity [E/e′] <13 both at rest and exercise; n = 63), C2 (E/e′ >13 only at exercise; n = 118), and C3 (E/e′ >13 both at rest and exercise; n = 26) HF. Exercise capacity and cardiovascular functional reserve were less impaired in stage C1 than in stages C2 and C3. Chronotropic response was more disturbed in stage C3 than C1 and C2. Changes from rest to exercise in E/e′ (−0.6 ± 1.7 vs. 3.7 ± 2.8; $p < 0.0001$), global longitudinal strain (2.9 ± 2.0 vs. 1.6 ± 2.8; $p < 0.002$), VAC (−0.21 ± 0.17 vs. −0.09 ± 0.15; $p < 0.0001$), and in VO_2-HR gradient (0.30 ± 0.07 vs. 0.26 ± 0.11; $p < 0.01$) were significantly different in stages B and C.

CONCLUSIONS Normal E/e′ response to exertion in symptomatic HFpEF is associated with less profound impairment of exercise capacity and is accompanied by derangements of contractile state and VAC. The transition from asymptomatic to overt HFpEF is linked to diastolic, systolic, and chronotropic deficits and an increasing degree of hemodynamic disturbances in stage C HF. (J Am Coll Cardiol 2016;67:659–70) © 2016 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) accounts for at least one-half of the total heart failure (HF) burden, and continues to account for a high rate of morbidity and mortality (1-3). The aging population and ongoing epidemics of obesity, type 2 diabetes mellitus, and hypertension will fuel the continued growth of HFpEF in the developed and developing worlds (1,4). HFpEF is of multifactorial etiology, and it has been proposed that separation of these mechanisms might be the key to finding more effective interventions (5-7). Although increased left ventricular (LV) stiffness and delayed relaxation lead to exercise limitation in HFpEF by restricting LV diastolic inflow and elevating LV filling pressure, diastolic dysfunction does not worsen during exercise in some patients (8,9). In addition to diastolic properties, HFpEF is attributable to the interaction of synergistic factors, including systolic performance, atrial mechanics, vascular stiffness, endothelial function,

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JACC VOL. 67, NO. 6, 2016
FEBRUARY 16, 2016:659–70

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

E = peak early diastolic mitral flow velocity

e′ = peak early diastolic mitral annular velocity

EAI = effective arterial elastance index

HFpEF = heart failure with preserved ejection fraction

HR = heart rate

LV = left ventricular

VAC = ventriculo-arterial coupling

VO_2 = oxygen uptake

ventriculo-arterial coupling (VAC), skeletal muscle oxygen extraction and oxidative metabolism, and autonomic nervous system regulation (5-7,10-14).

The factors responsible for the transition from an asymptomatic phase (stage B) of HFpEF to clinically overt HFpEF (stage C) and further progression of the disease are not well defined. Given the multiplicity of clinical and pathophysiological contributors, syndrome-associated disorders, and complications to the more complex stages of HFpEF (15-18), a study with special attention to an early phase of the disease may provide a more uniform subgroup to explore disease processes, as well as provide therapeutic targets with a potential for reversing the underlying processes. Accordingly, we sought to investigate the association of disturbances of various domains of cardiovascular function with impaired exercise tolerance across the spectrum of HFpEF in uncomplicated ("simple") disease. We hypothesized that reduction in contractile reserve, VAC reserve, and reduced chronotropic response were important determinants of decreased exercise capacity, irrespective of diastolic responses. To explore this, we recruited a group of subjects sharing a common demographic and disease profile with the symptomatic group, but with normal exercise tolerance, compatible with stage B. To evaluate the effect of these predictors on functional reserve, assessment was not limited to resting conditions, but was also performed under an exercise load.

SEE PAGE 671

METHODS

PATIENT SELECTION. We prospectively enrolled 207 consecutive patients satisfying the HFpEF criteria specified in current guidelines (19). These patients were characterized by:

1. Signs or symptoms of HF (dyspnea, fatigue and exercise intolerance) including New York Heart Association (NYHA) functional class II or III, defined by exercise capacity reduced >20% from age- and sex-predicted normal ranges;
2. Preserved LV ejection fraction (≥50%);
3. Diastolic dysfunction (20).

A total of 60 patients with a profile of underlying diseases analogous to the HFpEF group and with LV structural damage, as expressed by LV hypertrophy and/or reduced global longitudinal strain <18%, but with normal exercise tolerance (stage B HF) were also recruited from hospital clinics. All patients with stage B HF satisfied LV diastolic dysfunction criteria.

We excluded patients with atrial fibrillation or flutter; ischemic heart disease (defined by the presence of atherosclerotic lesions at coronary angiography in HFpEF patients or inducible ischemia during exercise testing in all participants); moderate and severe valvular heart disease; body mass index >36 kg/m^2; established or suspected pulmonary diseases (vital capacity <80% or forced expiratory volume in 1 s <80% of age- and sex-specific reference values); hemoglobin ≤11 g/dl; and other significant comorbidities, including malignancy, renal failure, infections, and autoimmune, skeletal, and thyroid illnesses. Although several of these features are associated with HFpEF, the rationale of their exclusion was that limitation of exercise tolerance posed by these additional burdens might confound the effects of cardiac abnormalities.

All participants were informed of the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the institutional ethics committee.

STUDY DESIGN. In this cross-sectional study, patients underwent cardiopulmonary exercise testing, resting and immediate post-exercise echocardiogram (including assessment of myocardial deformation), and blood sampling for laboratory assessments, including galectin-3 and B-type natriuretic peptide (BNP).

ECHOCARDIOGRAPHY. Echocardiographic imaging was performed using standard equipment (Vivid e9, General Electric Medical Systems, Milwaukee, Wisconsin) with phased array 2.5-MHz multifrequency transducers. Images were saved in digital format on a secure server for offline analysis. Assessments of cardiac dimensions and wall thicknesses, and left atrial volume (area-length method) were carried out according to standard recommendations (21). LV end-diastolic and -systolic volumes were measured in the apical 4- and 2-chamber views using the biplane Simpson method and were used for the calculation of ejection fraction. All cardiac volumes were indexed to body surface area and expressed as end-diastolic, end-systolic, and stroke volume indexes. Cardiac output was determined from the product of heart rate (HR) and stroke volume.

LV inflow parameters were evaluated by pulsed-wave Doppler from the apical 4-chamber view with the sample volume positioned between the tips of mitral leaflets, and included peak early (E) and late diastolic flow velocity (A), and deceleration time of

the E-wave. Pulsed-wave tissue Doppler was performed to establish peak early diastolic tissue velocity (e′) at the septal and lateral aspects of the mitral annulus. The ratio of mitral inflow early diastolic velocity to the average e′ velocity from the septal and lateral sides of the mitral annulus (E/e′) was calculated to estimate LV filling pressure. On the basis of previous validations, this was considered to be elevated at E/e′ >13 (20,22).

SPECKLE-TRACKING IMAGING. LV myocardial deformation was assessed using a semiautomated 2-dimensional speckle-tracking technique (Echopac version 113, General Electric Medical Systems) in the 3 apical views at a temporal resolution of 60 to 90 frames/s. After manually tracing the endocardial border and selecting the appropriate wall thickness, the software automatically identified 6 segments in each view and tracked the motion of acoustic markers. Segments with inadequate tracking were readjusted manually, and if this was ineffective, these segments were excluded from further analysis. Right ventricular (RV) deformation was evaluated from the RV-focused apical 4-chamber view, and RV strain was analyzed offline using the same software. The measurements comprised the greatest negative value on the strain curve and were presented as the averages from all segments interrogated.

The assessment of left atrial longitudinal strain was carried out in the apical 4- and 2-chamber views using the onset of the P-wave as the zero reference point, allowing measurements of deformation at atrial contraction (the first negative component) and total left atrial deformation (the sum of peak negative and peak positive components). All echocardiographic parameters were averaged over 3 consecutive cardiac cycles.

VENTRICULO-ARTERIAL COUPLING. This ratio was calculated as the quotient of effective arterial elastance index (EAI) and left ventricular end-systolic elastance index (ELVI), whereby EAI and ELVI were derived as the ratio of end-systolic pressure to stroke volume index and end-systolic volume index, respectively. End-systolic pressure was computed from the equation 0.9 × brachial systolic blood pressure, which accurately approximates invasive measurements of end-systolic pressure (23).

CARDIOPULMONARY EXERCISE TESTING. Symptom-limited exercise testing was performed on a treadmill using a modified Bruce protocol, and with standard cardiopulmonary stress equipment. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously, and peak oxygen uptake (peak VO_2) was calculated as the average oxygen consumption during the last 30 s of exercise. Exercise capacity was also evaluated in metabolic equivalents on the basis of the peak exercise intensity.

Echocardiographic assessment of wall motion, LV volumes, myocardial deformation, and diastolic function (including E/e′ ratio) was carried out before and immediately after cessation of exercise. This information was used to characterize subgroups of patients in stage C (**Central Illustration**). Transmitral flow and mitral annular velocities were measured after the acquisition of 2-dimensional loops. In case of fusion of early and late diastolic Doppler waves (E and A and/or e′ and a′) at high HRs, imaging was delayed until separation of these parameters.

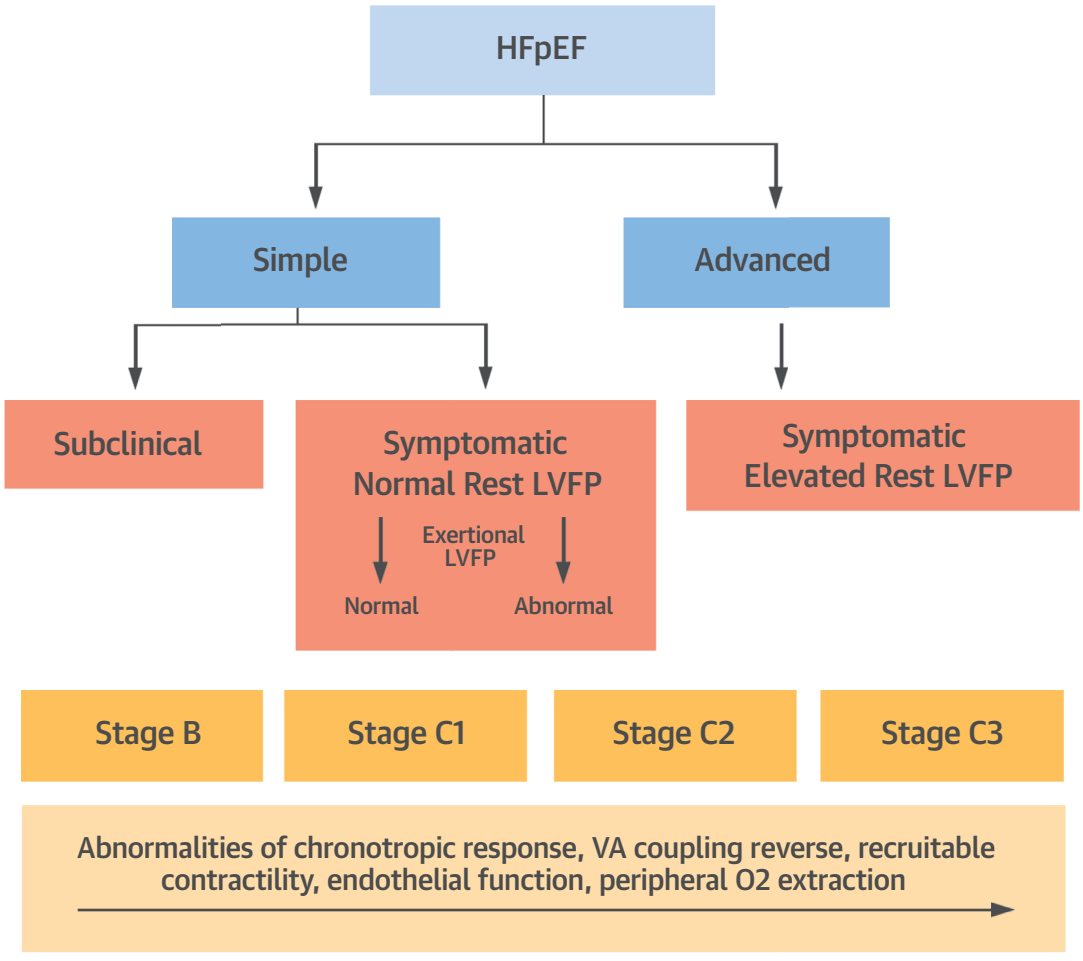
CHRONOTROPIC RESPONSE. HR reserve was determined as the change in HR from rest to peak exercise, expressed as a percentage of the predicted maximal HR reserve (calculated as a difference between the predicted maximal HR and the resting HR). A VO_2-HR gradient was obtained on the basis of the VO_2 and HR at each level of exercise.

BLOOD ASSAYS. Peripheral venous blood samples were collected between 8:00 AM and 9:00 AM, after 30 min of rest in the supine position, and then frozen at −70°C until assayed. Serum galectin-3 levels were measured using ELISA kits from BioVendor, Inc. (Brno, Czech Republic). Intra-assay and interassay coefficients of variation were 6.3% and 8.7%, respectively. BNP levels were assessed with a commercially available fluorescence immunoassay (Triage BNP Test, Biosite Diagnostics Inc., San Diego, California).

STATISTICAL ANALYSIS. Data are presented as mean ± SD or as median (interquartile range) for continuous variables, and as counts and percentages for categorical variables. Between-group comparisons were performed with an unpaired 2-sided Student *t* test or, when more than 2 groups were included, by 1-way analysis of variance, with the Scheffe post hoc test for continuous variables and the chi-square test for categorical variables. Homogeneity of variances was evaluated by the Levene test. Associations between variables were assessed by Pearson correlation coefficient and stepwise multiple regression analysis. Skewed variables were analyzed after log transformation. Receiver-operating characteristic (ROC) analysis was used to evaluate the ability of particular variables to predict impaired exercise capacity. Differences in the area under the receiver-operating characteristic curves (AUCs) were analyzed using the z-test. Changes in particular parameters with exercise were calculated by subtracting the pre-test value from the post-test value and were expressed in the units of their measurements. The reproducibility of

JACC VOL. 67, NO. 6, 2016
FEBRUARY 16, 2016:659–70

CENTRAL ILLUSTRATION **Nondiastolic Factors in HFpEF: Classification of HFpEF According to the Complexity of Clinical Presentation**



Kosmala, W. et al. J Am Coll Cardiol. 2016; 67(6):659-70.

Heart failure with preserved ejection fraction (HFpEF) may be classified according to symptom status, rest, and exercise elevation of left ventricular filling pressure (LVFP). More extensive physiological derangements are associated with more symptoms and more persistent elevations of filling pressure.

echocardiographic measurements was evaluated by the Bland-Altman method (mean difference and 95% confidence interval [CI]), intraclass correlation coefficient (ICC), and coefficient of variation. All calculations were carried out using standard statistical software (Statistica for Windows 10, StatSoft Inc., Tulsa, Oklahoma). The level of statistical significance was set at a 2-sided p value <0.05.

RESULTS

PATIENT CHARACTERISTICS. The clinical profile of patients, both with and without exercise intolerance, was characterized by the predominance of hypertension, overweight, and diabetes mellitus. To distinguish the contribution of exercise-induced diastolic abnormalities to reduced functional capacity, patients with exercise intolerance (stage C) were divided into 3 subgroups, representing the 3 levels of increasing severity of physiological disturbances (Central Illustration). Stage C1 was defined by $E/e' <13$, both at rest and at exercise ($n = 63$), stage C2 by $E/e' >13$ only at exercise ($n = 118$), and stage C3 by $E/e' >13$ both at rest and at exercise ($n = 26$). Resting diastolic abnormalities in the C3 group were categorized as grade I dysfunction in 11 patients, grade II in 11 patients, and

grade IIIa (reversible restriction, verified by the Valsalva maneuver) in 4 patients. On the basis of these definitions, exercise capacity (peak VO_2 and estimated metabolic equivalents) was significantly lower in stage C than in stage B, and decreased progressively from the C1 to C2 to C3 group. Correspondingly, the progressive increase in the proportion of patients with signs or symptoms of HF and hospitalization for HF within the last 12 months was noted across the stage C groups. No differences between stages B and C or among the stage C subgroups were found for rest and peak exercise blood pressure, hemoglobin, and medical therapy, except for a lower prevalence of diuretic agents in pre-clinical disease and a higher frequency in the C3 group. Creatinine level was higher in stage C than in stage B. HR reserve was significantly reduced in stage C as compared with asymptomatic patients and in the C2 and C3 groups in comparison with the C1 group. The VO_2-HR gradient was significantly lower in stage C than B and in the C3 group than in the other stage C subsets. BNP was only elevated in the C3 group. Circulating galectin-3 was higher in stage C than B and in the C2 and C3 groups than in the C1 group (Tables 1 and 2).

CARDIAC STRUCTURE AND RESTING FUNCTION. LV mass and left atrial size were both significantly higher in stage C than B. The C3 group was characterized by larger LV mass, interventricular septum thickness, and left atrial size than in the other stage C groups. No significant differences with respect to LV diastolic size or posterior wall thickness were found between stages B and C and among all 3 stage C groups (Tables 3 and 4).

Global LV longitudinal deformation, left atrial deformation, and e′ were significantly lower, and E/e′ and deceleration time of early mitral inflow were higher in stage C than B. There were gradations of e′, E/e′, and deformation components in the stage C groups, but no differences between stages B and C and across the stage C subgroups in resting values of LV end-systolic volume index, stroke volume index, cardiac output, ejection fraction, VAC, ELVI, and EAI (Tables 5 and 6).

CARDIOVASCULAR FUNCTION–RESPONSE TO EXERCISE. The response of cardiovascular function to exertion was more impaired in stage C than B and in the C2 and C3 groups than in the C1 group. These changes included disturbances of exercise responses of e′, LV longitudinal deformation, LV elastance, and VAC in stage C compared with stage B. The comparative analysis across the stage C subgroups revealed significant differences in exertional responses in the C2 and C3 groups in comparison with the C1 group; in particular, the increase in longitudinal deformation during exercise was lower in the C2 group than in the C1 group (Table 6). ROC analysis was employed to assess the associations of the diagnosis of stage C HF. Comparisons of the AUCs revealed that the predictive value progressively increased from VO_2-HR gradient (AUC: 0.65) through ΔVAC (AUC: 0.71), Δcardiac output (AUC: 0.75), HR reserve (AUC: 0.76), and to exertional strain (AUC: 0.78) (Figure 1).

REPRODUCIBILITY. The variability of echocardiographic measurements was assessed in 15 randomly selected examinations and was analyzed twice by 2 observers (W.K. and A.R.) blinded to patient clinical data on 2 separate days with a 2-week time interval (Table 7).

TABLE 1 Demographic, Clinical, and Cardiopulmonary Exercise Testing Characteristics in Asymptomatic (Stage B) and Symptomatic (Stage C) HFpEF

	Stage B (n = 60)	Stage C (n = 207)	p Value
Age, yrs	62.8 ± 7.5	63.7 ± 8.6	0.49
Female	40 (67)	152 (73)	0.31
BMI, kg/m^2	27.6 ± 3.7	29.6 ± 4.1	0.002
DM	16 (27)	69 (33)	0.33
HT	54 (90)	184 (89)	0.81
SBP at rest, mm Hg	127 ± 14	129 ± 16	0.54
DBP at rest, mm Hg	76 ± 9	75 ± 9	0.40
Exercise SBP, mm Hg	165 ± 23	164 ± 22	0.81
Exercise DBP, mm Hg	68 ± 13	67 ±12	0.41
Heart rate reserve, %	87 ± 20	65 ± 22	0.0001
Gradient VO_2-HR	0.30 ± 0.07	0.26 ± 0.11	0.01
Peak VO_2, ml/min/kg	22.3 ± 4.1	15.5 ± 4.7	0.0001
Peak VO_2 % predicted	94 ± 10	63 ± 13	0.0001
MET	8.9 ± 2.7	5.4 ± 2.8	0.0001
BNP, pg/ml	38 (19-65)	44 (19-107)	0.34
Galectin-3, ng/ml	0.93 (0.72-1.33)	1.30 (0.86-2.16)	0.004
Hemoglobin, g/dl	13.9 ± 1.1	13.6 ± 1.1	0.12
Creatinine, mg/dl	0.95 ± 0.14	1.03 ± 0.26	0.03
Beta-blockers	38 (63)	150 (72)	0.18
Calcium-channel blockers	18 (30)	78 (38)	0.28
ACEI/ARB	53 (88)	194 (94)	0.17
Diuretics	23 (38)	136 (66)	0.001
Thiazides	23 (38)	104 (50)	0.11
Loop diuretics	0 (0)	32 (15)	–
Oral hypoglycemic drugs	13 (22)	61 (29)	0.24

Values are mean ± SD, n (%), or median (interquartile range).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; DM = diabetes mellitus; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; HT = arterial hypertension; LV = left ventricular; MET = metabolic equivalent; SBP = systolic blood pressure; VO_2 = oxygen uptake.

DISCUSSION

This study demonstrates that multiple cardiovascular abnormalities underlie exercise limitation in patients

JACC VOL. 67, NO. 6, 2016
FEBRUARY 16, 2016:659–70

TABLE 2 Demographic, Clinical, and Cardiopulmonary Exercise Testing Characteristics Across the Stages of Symptomatic HFpEF

	Stage C1 (n = 63)	Stage C2 (n = 118)	Stage C3 (n = 26)	p Value		
				C1 vs. C2	C1 vs. C3	C2 vs. C3
Age, yrs	61.4 ± 8.2	63.7 ± 8.3	68.9 ± 9.2	0.07	0.0002	0.04
Female	42 (67)	90 (76)	20 (77)	0.17	0.34	0.94
BMI, kg/m^2	29.4 ± 3.9	29.7 ± 4.2	29.5 ± 4.2	0.55	0.89	0.77
DM	18 (29)	39 (33)	12 (46)	0.54	0.11	0.21
HT	53 (84)	106 (90)	25 (96)	0.26	0.12	0.31
SBP at rest, mm Hg	125 ± 13	130 ± 18	131 ± 12	0.20	0.26	0.89
DBP at rest, mm Hg	75 ± 9	76 ± 10	75 ± 9	0.81	0.98	0.86
Exercise SBP, mm Hg	159 ± 20	167 ± 23	163 ± 19	0.13	0.85	0.74
Exercise DBP, mm Hg	66 ±12	67 ± 12	66 ± 12	0.73	0.97	0.95
Heart rate reserve, %	73 ± 23	63 ± 21	59 ± 21	0.004	0.005	0.37
Gradient VO_2-HR	0.27 ± 0.11	0.27 ± 0.11	0.21 ± 0.10	0.95	0.04	0.03
Peak VO_2, ml/min/kg	17.6 ± 4.7	14.9 ± 4.3	12.9 ± 5.0	0.0002	0.0001	0.05
Peak VO_2 % predicted	68 ± 11	61 ± 12	61 ± 16	0.0005	0.006	0.89
MET	6.5 ± 2.9	5.1 ± 2.8	4.2 ± 2.2	0.003	0.0007	0.13
BNP, pg/ml	33 (14–84)	38 (19–85)	106 (52–164)	0.94	0.001	0.001
Galectin-3, ng/ml	0.90 (0.76–1.15)	1.72 (1.10–2.35)	1.45 (0.86–2.24)	0.0001	0.02	0.28
Hemoglobin, g/dl	13.8 ± 1.3	13.5 ± 1.0	13.7 ± 0.9	0.38	0.95	0.91
Creatinine, mg/dl	1.04 ± 0.30	1.01 ± 0.24	1.10 ± 0.31	0.93	0.80	0.47
Exertional dyspnea	63 (100)	118 (100)	26 (100)	–	–	–
Peripheral edema and/or pulmonary congestion	8 (13)	31 (26)	14 (54)	0.04	0.0001	0.006
Fatigue	21 (33)	72 (61)	20 (77)	0.0004	0.0002	0.12
Hospitalization for heart failure (last 12 months)	13 (21)	54 (46)	18 (69)	0.001	0.0001	0.03
Beta-blockers	41 (65)	88 (75)	21 (81)	0.18	0.15	0.51
Calcium-channel blockers	26 (41)	42 (36)	10 (38)	0.45	0.81	0.79
ACEI/ARB	58 (92)	112 (95)	24 (92)	0.44	0.97	0.60
Diuretic agents	39 (62)	74 (63)	23 (88)	0.91	0.02	0.02
Thiazides	31 (49)	59 (50)	14 (54)	0.92	0.69	0.73
Loop diuretic agents	8 (13)	15 (13)	9 (34)	0.99	0.02	0.007
Oral hypoglycemic drugs	15 (24)	37 (31)	9 (34)	0.29	0.30	0.75

Values are mean ± SD, n (%), or median (interquartile range).

C1 = heart failure with preserved ejection fraction patients without exercise-induced increase in LV filling pressure (E/e′ <13); C2 = heart failure with preserved ejection fraction patients with exercise-induced increase in LV filling pressure (E/e′ > 13); C3 = heart failure with preserved ejection fraction with elevated LV filling pressure (E/e′>13) both at rest and exercise; other abbreviations as in Table 1.

with uncomplicated HFpEF. Although an exertional increase in E/e′ suggesting elevation of LV filling pressure is the major contributor, this is absent in about 35% of cases. In the presence of normal LV diastolic response to exertion, exercise capacity is less compromised and partly determined by reduced recruitable contractility and ventriculo-arterial coupling reserve. Diastolic, systolic, and chronotropic derangements are linked with the transition from asymptomatic to clinically overt HFpEF, as well as with increasing severity of hemodynamic disturbances in stage C.

CONTRIBUTORS TO REDUCED EXERCISE CAPACITY. In this study, entry criteria were specified to minimize the confounding effect of comorbidities and complications of HFpEF (e.g., coronary artery disease, pulmonary hypertension, atrial fibrillation, chronic kidney disease, and severe obesity). According to a commonly accepted definition, the presence

TABLE 3 Cardiac Structural and Functional Characteristics Assessed Only at Rest in Asymptomatic (Stage B) and Symptomatic (Stage C) HFpEF

	Stage B (n = 60)	Stage C (n = 207)	p Value
LVEDD, mm	49 ± 4	49 ± 4	0.35
IVS, mm	11.8 ± 1.3	12.3 ± 2.2	0.11
LVPW, mm	9.2 ± 1.2	9.4 ± 1.5	0.24
LVMI, g/m$^{2.7}$	49 ± 10	54 ± 13	0.005
LA diameter, mm	39.3 ± 4.5	42.2 ± 4.7	0.0001
LAVI, ml/m^2	28.6 ± 7.6	33.7 ± 9.6	0.0001
Total LA strain	38.0 ± 10.8	29.0 ± 8.8	0.0001
LA strain at atrial contraction	18.3 ± 5.4	14.6 ± 5.0	0.0001
Global RV strain	28.9 ± 5.8	27.2 ± 7.3	0.15

Values are mean ± SD.

HFpEF = heart failure with preserved ejection fraction; IVS = interventricular septum thickness; LA = left atrial; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVMI = left ventricular mass index; LVPW = left ventricular posterior wall thickness; RV = right ventricular.

TABLE 4 Cardiac Structural and Functional Characteristics Assessed Only at Rest Across the Stages of Symptomatic HFpEF

	Stage C1 (n = 63)	Stage C2 (n = 118)	Stage C3 (n = 26)	p Value		
				C1 vs. C2	C1 vs. C3	C2 vs. C3
LVEDD, mm	50 ± 4	49 ± 4	50 ± 5	0.51	0.83	0.74
IVS, mm	12.0 ± 2.1	12.2 ± 2.1	13.6 ± 2.8	0.85	0.01	0.01
LVPW, mm	9.3 ± 1.6	9.4 ± 1.4	10.0 ± 1.5	0.89	0.22	0.20
LVMI, g/m$^{2.7}$	52 ± 12	53 ± 13	63 ± 14	0.85	0.002	0.003
LA diameter, mm	41.3 ± 4.4	42.1 ± 4.9	45.4 ± 4.0	0.30	0.01	0.04
LAVI, ml/m^2	30.8 ± 7.7	33.5 ± 9.2	41.0 ± 11.9	0.14	0.0001	0.0004
Total LA strain	31.6 ± 9.8	28.9 ± 7.0	22.3 ± 7.4	0.11	0.0002	0.007
LA strain at atrial contraction	15.8 ± 5.4	14.6 ± 4.0	11.0 ± 5.4	0.19	0.0006	0.009
Global RV strain	27.4 ± 6.2	28.0 ± 7.9	22.9 ± 4.7	0.62	0.01	0.002

Values are mean ± SD.
Abbreviations as in Tables 2 and 3.

of diastolic dysfunction is a prerequisite for the diagnosis of HFpEF (19). Nonetheless, this finding is common in the absence of HFpEF, and may not be a pivotal reason for reduced exercise capacity in some patients. Notwithstanding the multiplicity of factors forming the pathophysiological framework of HFpEF, worsening LV diastolic filling during exercise is of central relevance for eliciting exertional intolerance in HFpEF (8,22,24,25). The morphological substrate for the exercise-induced increase in LV filling pressure is provided by enhanced LV stiffness, caused by exaggerated interstitial deposition and qualitative changes of collagen, as well as modifications in myocardial cytoskeletal proteins, especially titin (26–28). In the present study, HFpEF patients exhibiting exacerbation of diastolic abnormalities on exertion (as evidenced by E/e′ ratio >13) were characterized by more complex disease with lower functional capacity, which underpins the importance of this mechanism of exercise limitation. The finding of increased galectin-3 only in patients with exercise E/e′ >13 implies that this biomarker may have utility in quantification of disease severity, although this needs further assessment in view of the limited specificity of galectin-3 in HFpEF (29).

NONDIASTOLIC FACTORS. The distinction of a subset of HFpEF patients with an apparent predominance of nondiastolic factors emphasizes the need to accurately recognize these contributors in the selection of medical treatment. The inability to develop a sufficient increase in HR during exercise, with subsequent impairment of cardiac output reserve, was demonstrated progressively from the stage C1 to the stage C3 groups, and is thought to be due to blunted baroreflex sensitivity and autonomic dysfunction of peripheral (rather than central) origin (6,30). However, this finding might be either a cause or an adaptive alteration enabling prolongation of LV filling with lower HR. The decrease in exertional peak HR may not be only due to the aforementioned reasons, but may also simply reflect a premature termination of exercise caused by other mechanisms. Therefore, HR reserve might not adequately express actual chronotropic abnormalities. The VO_2-HR gradient, a more specific marker of the relationship between exercise capacity and exertional increments in HR, confirmed the association of inadequate chronotropic response with exercise limitation.

Despite its nomenclature, HFpEF is associated with impaired myocardial contractility, the severity of which correlates with mortality (10). Although the effect of these findings on exercise intolerance was previously uncertain (10–12,31,32), this study demonstrated decreased LV longitudinal deformation, both at rest and after exercise, as well as an attenuated exertional increase in global LV ejection fraction in all 3 stage C groups. Inadequate decrease in end-systolic volume at exercise, especially evident in patients with a more complex disease, is likely to be due to contractile reserve limitation, given the absence of significant between-group differences in blood pressure and arterial elastance. Putative mechanisms behind diminished contractile reserve in HFpEF encompass decreased sensitivity to beta-adrenergic stimulation, abnormalities of cardiomyocyte calcium handling, and deficient myocardial energetic status (11,12,33). The role of LV pump efficiency in limiting exercise performance in HFpEF, especially with more severe functional impairment, was also evinced by lower cardiac output reserve. However, diminished exertional increase in cardiac output in stage C was mainly due to the reduction in chronotropic reserve, as there were no significant intergroup differences in stroke volume from stage B through stages C1 to C2 and C3.

TABLE 5 Cardiovascular Characteristics Assessed at Rest and Post-Exercise in Asymptomatic (Stage B) and Symptomatic (Stage C) HFpEF

	Stage B (n = 60)	Stage C (n = 207)	p Value
E/A			
Rest	1.02 ± 0.32	0.95 ± 0.46	0.29
Post-ex	1.02 ± 0.25	1.23 ± 0.51	0.003
Δ	0.01 ± 0.24	0.29 ± 0.31	0.0001
DT, ms			
Rest	208 ± 43	232 ± 47	0.001
Post-ex	144 ± 31	165 ± 37	0.0001
Δ	−64 ± 45	−65 ± 46	0.85
e′ sept, cm/s			
Rest	7.6 ± 1.9	5.8 ± 1.3	0.0001
Post-ex	10.4 ± 2.3	7.1 ± 1.8	0.0001
Δ	2.8 ± 1.7	1.2 ± 1.2	0.0001
E/e′			
Rest	9.7 ± 1.7	11.6 ± 3.6	0.0001
Post-ex	9.0 ± 1.9	15.3 ± 5.0	0.0001
Δ	−0.6 ± 1.7	3.7 ± 2.8	0.0001
GLS, %			
Rest	20.4 ± 2.2	18.4 ± 3.3	0.0001
Post-ex	23.3 ± 2.6	20.0 ± 3.5	0.0001
Δ	2.9 ± 2.0	1.6 ± 2.8	0.002
LVEDVI, ml/m^2			
Rest	46 ± 9	43 ± 11	0.09
Post-ex	46 ± 8	44 ± 11	0.23
Δ	−0.6 ± 4.1	1.4 ± 6.5	0.04
LVESVI, ml/m^2			
Rest	14 ± 6	12 ± 6	0.08
Post-ex	9 ± 3	11 ± 5	0.01
Δ	−5.1 ± 4.1	−1.5 ± 3.4	0.0001
SVI, ml/m^2			
Rest	33 ± 6	31 ± 7	0.18
Post-ex	37 ± 6	34 ± 9	0.02
Δ	4.5 ± 4.8	3.0 ± 6.4	0.10
CO, l/min			
Rest	4.5 ± 1.3	4.2 ± 1.2	0.12
Post-ex	10.0 ± 2.5	8.0 ± 2.8	0.0001
Δ	5.5 ± 1.7	3.8 ± 2.4	0.0001
LVEF, %			
Rest	71 ± 9	72 ± 9	0.29
Post-ex	81 ± 6	76 ± 8	0.0001
Δ	10.4 ± 8.1	4.3 ± 7.3	0.0001
VAC			
Rest	0.45 ± 0.19	0.41 ± 0.18	0.16
Post-ex	0.25 ± 0.09	0.32 ± 0.14	0.0004
Δ	−0.21 ± 0.17	−0.09 ± 0.15	0.0001
ELVI, mm Hg/ml/m^2			
Rest	10.0 ± 5.2	10.8 ± 4.7	0.27
Post-ex	20.8 ± 12.1	16.9 ± 10.2	0.02
Δ	10.8± 8.3	6.1 ± 8.3	0.0002
EAI, mm Hg/ml/m^2			
Rest	3.7 ± 0.9	4.0 ± 1.0	0.07
Post-ex	4.3 ± 1.1	4.5 ± 1.2	0.27
Δ	0.6 ± 0.7	0.5 ± 0.9	0.59

Values are mean ± SD.

A = late diastolic mitral flow velocity; CO = cardiac output; Δ = value post-exercise minus value at rest; DT = deceleration time of E-wave; E = peak early diastolic mitral flow velocity; e′ = peak early diastolic mitral annular velocity; EAI = effective arterial elastance index; ELVI = left ventricular end-systolic elastance index; GLS = global longitudinal strain; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; post-ex = post exercise; SVI = stroke volume; VAC = ventriculo-arterial coupling.

The interaction between the heart and the systemic vasculature (VAC) is an important determinant of efficient cardiac work. It incorporates 2 components: arterial elastance, a measure of stiffness of the arterial tree and afterload, and LV end-systolic elastance, a measure of systolic stiffness of the left ventricle and contractility. An attenuation of the normal decrement in VAC during exercise in HFpEF patients (5,12) was independently associated with peak oxygen consumption, confirming its detrimental role in exertional limitation. The blunted exercise increment in LV end-systolic elastance in HFpEF patients with exertional E/e′ >13, which is responsible for impaired VAC exertional response, possibly reflects less physiological augmentation of LV contractile state resulting from more severe myocardial impairment in this subgroup.

Our work supports and extends previously reported hypotheses and findings on the significance of chronotropic and contractile deficits in HFpEF by using a larger sample size and more comprehensive methods, staging, and categorization to assess the association of these derangements with HFpEF severity (5).

HFpEF PATIENTS WITHOUT EXERCISE INCREMENT OF ESTIMATED LV FILLING PRESSURE. The heterogeneity of this illness is likely an important contributor to the difficulty in identifying effective treatments that work across the range of HFpEF. Therapies improving diastolic filling might be reasonable only in selected HFpEF patients. For example, exercise-induced increases in LV filling pressure might reflect reduced LV compliance. In this setting, HFpEF may be amenable to therapy targeted at reducing myocardial fibrosis. Conversely, the most important contributors to reduced exercise capacity in the group without an abnormal diastolic response to exercise include decreased longitudinal deformation, ejection fraction, and VAC reserve.

Our results suggest that patients with functional intolerance, but no evidence of worsening diastolic

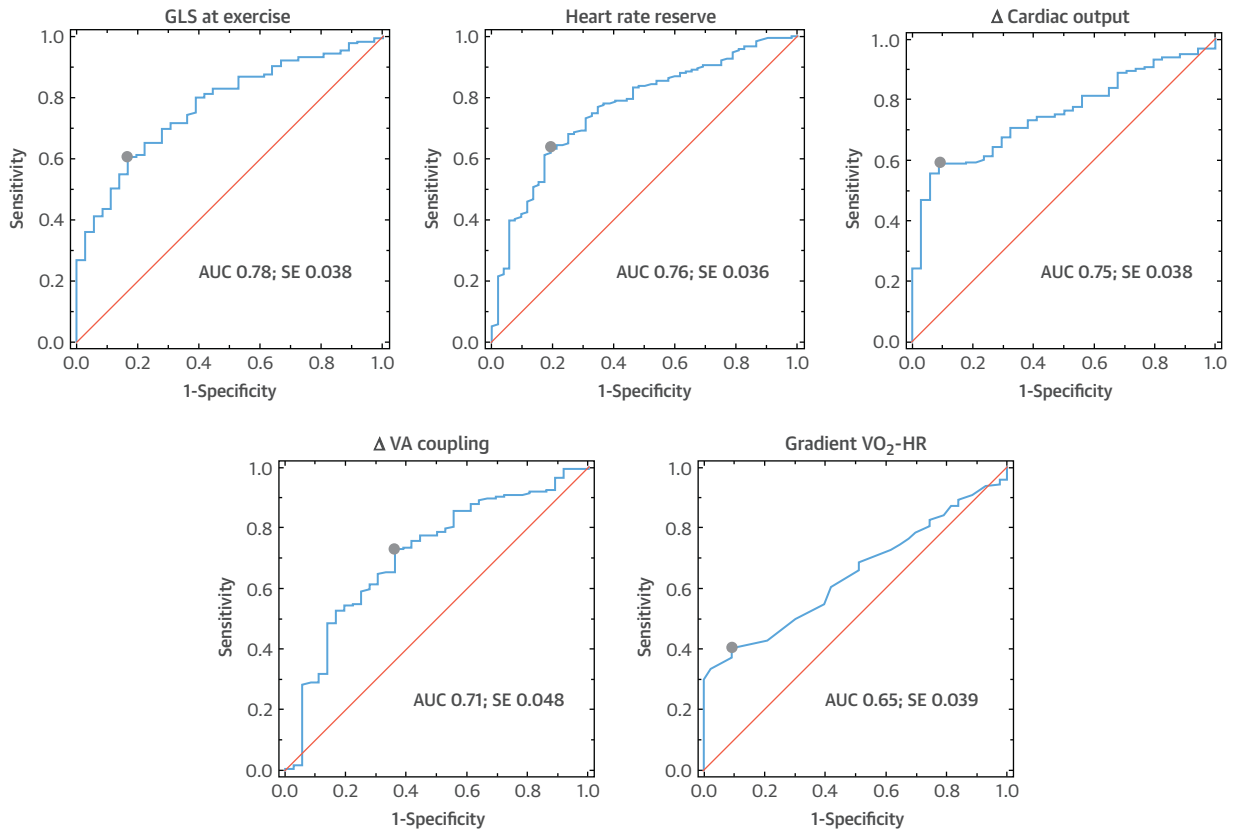
TABLE 6 Cardiovascular Characteristics Assessed at Rest and Post-Exercise Across the Stages of Symptomatic HFpEF

	Stage C1 (n = 63)	Stage C2 (n = 118)	Stage C3 (n = 26)	p Value		
				C1 vs. C2	C1 vs. C3	C2 vs. C3
E/A						
Rest	0.87 ± 0.29	0.85 ± 0.26	1.52 ± 0.86	0.60	0.0001	0.0001
Post-ex	0.95 ± 0.24	1.23 ± 0.42	1.75 ± 0.81	0.0006	0.0001	0.0001
Δ	0.09 ± 0.21	0.37 ± 0.29	0.23 ± 0.40	0.0001	0.05	0.02
DT, ms						
Rest	228 ± 48	236 ± 43	221 ± 58	0.38	0.77	0.29
Post-ex	160 ± 32	173 ± 35	154 ± 46	0.38	0.95	0.22
Δ	−68 ± 47	−63 ± 45	−67 ± 47	0.66	0.89	0.60
e′ sept, cm/s						
Rest	6.3 ± 1.3	5.8 ± 1.2	5.0 ± 1.3	0.02	0.0001	0.009
Post-ex	8.3 ± 1.9	6.8 ± 1.5	5.9 ± 1.6	0.0001	0.0001	0.02
Δ	2.0 ± 1.6	1.0 ± 1.0	0.9 ± 0.9	0.0001	0.0007	0.66
E/e′						
Rest	9.6 ± 1.6	10.8 ± 1.6	18.4 ± 4.7	0.0006	0.0001	0.0001
Post-ex	10.0 ± 1.6	15.6 ± 2.5	23.5 ± 5.3	0.0001	0.0001	0.0001
Δ	0.4 ± 2.1	4.7 ± 2.0	5.1 ± 2.8	0.0001	0.0001	0.36
GLS, %						
Rest	18.7 ± 3.0	18.6 ± 3.2	17.2 ± 4.3	0.78	0.09	0.08
Post-ex	21.4 ± 3.3	19.7 ± 3.1	19.4 ± 5.0	0.009	0.02	0.67
Δ	2.7 ± 2.9	1.2 ± 2.7	2.2 ± 2.4	0.003	0.43	0.10
LVEDVI, ml/m^2						
Rest	43 ± 10	43 ± 9	47 ± 12	0.85	0.28	0.08
Post-ex	43 ± 10	44 ± 10	48 ± 11	0.92	0.20	0.21
Δ	−0.05 ± 5.4	1.9 ± 6.3	1.2 ± 7.0	0.25	0.73	0.90
LVESVI, ml/m^2						
Rest	12 ± 6	12 ± 5	13 ± 8	0.81	0.49	0.31
Post-ex	9 ± 4	11 ± 5	12 ± 6	0.04	0.01	0.25
Δ	−3.2 ± 4.3	−1.1 ± 3.3	−1.1 ± 3.7	0.002	0.03	0.93
SVI, ml/m^2						
Rest	31 ± 7	30 ± 7	33 ± 8	0.54	0.68	0.09
Post-ex	34 ± 9	33 ± 8	36 ± 12	0.54	0.27	0.08
Δ	3.2 ± 6.5	3.0 ± 6.0	2.4 ± 8.0	0.90	0.65	0.67
CO, l/min						
Rest	4.3 ± 1.3	4.1 ± 1.3	4.1 ± 1.1	0.25	0.46	0.96
Post-ex	8.5 ± 2.8	7.9 ± 2.8	7.9 ± 3.1	0.37	0.46	0.94
Δ	4.3 ± 2.5	3.8 ± 2.3	3.7 ± 2.7	0.20	0.27	0.87
LVEF, %						
Rest	72 ± 8	72 ± 8	73 ± 10	0.76	0.79	0.58
Post-ex	79 ± 8	76 ± 7	75 ± 8	0.009	0.04	0.84
Δ	6.9 ± 8.8	3.8 ± 6.7	2.4 ± 6.3	0.03	0.02	0.39
VAC						
Rest	0.40 ± 0.17	0.41 ± 0.18	0.40 ± 0.22	0.75	0.99	0.78
Post-ex	0.27 ± 0.13	0.34 ± 0.14	0.34 ± 0.14	0.01	0.04	0.84
Δ	−0.13 ± 0.17	−0.07 ± 0.13	−0.06 ± 0.15	0.08	0.09	0.62
ELVI, mm Hg/ml/m^2						
Rest	10.5 ± 5.2	11.0 ± 4.6	10.5 ± 4.6	0.61	0.98	0.67
Post-ex	20.7 ± 14.6	16.3 ± 8.6	13.2 ± 6.0	0.04	0.02	0.28
Δ	10.2 ± 12.8	5.2 ± 6.4	2.8 ± 2.8	0.006	0.005	0.27
EAI, mm Hg/ml/m^2						
Rest	3.9 ± 0.9	4.2 ± 1.0	3.6 ± 0.8	0.34	0.80	0.09
Post-ex	4.3 ± 1.3	4.7 ± 1.1	4.0 ± 1.2	0.43	0.81	0.12
Δ	0.5 ± 0.9	0.5 ± 0.9	0.4 ± 0.8	0.87	0.88	0.76

Values are mean ± SD.

Abbreviations as in Tables 2 and 5.

FIGURE 1 Receiver-Operator Characteristic Curves of GLS at Exercise, HR Reserve, VA Coupling Reserve, and Gradient VO_2-HR in Predicting Stage C HFpEF



The optimal cutpoints are displayed as **solid circles**. Significant differences in AUCs: GLS versus gradient VO_2-HR p = 0.02; and HR reserve versus gradient VO_2-HR p = 0.045. AUC = area under the curve; CO = cardiac output; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; VA = ventriculo-arterial; VO_2 = oxygen uptake.

function with exercise, might represent an intermediate stage in the transition to more complex disease. This hypothesis is supported by the trend of deteriorating exercise capacity and cardiovascular characteristics in the stages of development of HF, ranging from asymptomatic patients with LV impairment, categorized as stage B, to patients with less (C1) and more (C2 and C3) severe exercise limitation. Extended follow-up in this "less complex" HFpEF group would be of value to provide information on the possible progression of exertional diastolic abnormalities.

TRANSITION FROM STAGE B TO C HFpEF. The appearance of the symptomatic disease phase is associated with worse prognosis and necessitates a change in treatment. Both diastolic and nondiastolic factors seem to contribute to symptoms of exertional dyspnea, as evidenced by significant differences between stages B and C in change from rest to exercise in E/e′, global longitudinal strain, LV ejection fraction, and VAC, as well as inadequate chronotropic response, marked particularly in more profound hemodynamic disturbances (stage C3). This finding extends existing knowledge of the development of stage C HFpEF by underpinning the role of contractile abnormalities as 1 of the drivers and may provide some therapeutic implications.

In this study, BNP levels measured in resting conditions were raised only in patients with complex HFpEF from group C3, that is, with baseline E/e′ >13 and further increase in E/e′ during exercise, which is consistent with previous invasive investigations (34). This observation is compatible with a greater severity of myocardial dysfunction in this group and underlines the challenge of applying cutpoints of resting BNP measurements to the identification of HFpEF (35).

TABLE 7 Reproducibility of Echocardiographic Parameters

	Bland–Altman		ICC		Coefficient of Variation	
	Intraobserver	Interobserver	Intraobserver	Interobserver	Intraobserver	Interobserver
GLS						
Rest	0.2 (−0.2 to 0.6)	−0.3 (−1.3 to 0.7)	0.94	0.91	3.5	5.6
Exercise	0.5 (−0.3 to 1.3)	0.9 (−0.3 to 2.1)	0.97	0.93	4.0	6.0
E/e′						
Rest	0.7 (0.3 to 1.2)	−0.2 (−0.6 to 0.2)	0.94	0.89	4.7	6.1
Exercise	−0.4 (−1.0 to 0.3)	−0.8 (−1.3 to −0.3)	0.94	0.96	5.6	6.7
LVEDV						
Rest	−0.5 (−7.9 to 6.9)	1.5 (−6.2 to 9.2)	0.92	0.89	5.8	6.7
Exercise	0.8 (−4.0 to 5.5)	2.9 (−6.1 to 11.8)	0.90	0.88	7.0	7.8
LVESV						
Rest	0.8 (−2.5 to 4.1)	1.1 (−3.2 to 5.4)	0.89	0.86	8.6	9.3
Exercise	0.9 (−2.1 to 3.9)	1.4 (−3.1 to 5.9)	0.93	0.90	7.2	8.3

ICC = intraclass correlation coefficient; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Table 5.

STUDY LIMITATIONS. This study should be considered in the light of 6 limitations. First, this analysis does not consider a number of potential determinants of exercise capacity in HFpEF, including endothelial dysfunction, passive cardiomyocyte elasticity, peripheral oxygen extraction (36), and pulmonary vascular dysfunction (37). Second, measurements of LV circumferential and radial deformation, as well as rotational mechanics, were not reliable in exercise acquisitions due to through-plane motion. Third, no invasive verification of LV filling pressure was undertaken. Fourth, despite the absence of significant between-group differences in the prescription of beta-blockers, their potential effect on the analysis of chronotropic response should be acknowledged. Fifth, exclusion of patients with substantial obesity, although justified by reduction of extracardiac effects of weight excess on exercise tolerance, might have narrowed the spectrum of HFpEF patients. Finally, all enrollees were Caucasian; therefore, extrapolation of the present findings to other ethnic groups should be made with caution.

CONCLUSIONS

LV diastolic, systolic, and chronotropic abnormalities are associated with the shift from stage B to C HFpEF and with increasing degree of hemodynamic disturbances in the symptomatic phase. The absence of an exercise-induced increment of estimated LV filling pressure in symptomatic early-stage HFpEF is associated with less profound impairment of exercise capacity. Derangements of contractile state and VAC should be considered as underlying mechanisms of exercise limitation in this setting. Recognition of specific patterns of abnormal cardiovascular responses to exertion may define more targeted and individualized treatment strategies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFpEF often involves diastolic dysfunction, but raised filling pressures are not the only cause of exercise limitation. Recruitable contractility, arterial-ventricular coupling reserve, and chronotropic response are important contributors to exercise intolerance.

TRANSITIONAL OUTLOOK: Better characterization of the mechanisms contributing to this heterogeneous phenotype may improve the ability to provide targeted therapies for patients with HFpEF.

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