

Exercise Limitation Associated With Asymptomatic Left Ventricular Impairment

Analogy With Stage B Heart Failure

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ABSTRACT

BACKGROUND Stage B heart failure (SBHF) describes asymptomatic ventricular disease that may presage the development of heart failure (HF) symptoms. This entity has been largely defined by structural changes; the roles of sensitive indicators of nonischemic left ventricular (LV) dysfunction, such as LV strain, are undefined.

OBJECTIVES This study sought to define the association of exercise capacity with left ventricular hypertrophy (LVH) and systolic/diastolic dysfunction in asymptomatic patients with HF risk factors.

METHODS We used echocardiography to study 510 asymptomatic patients (age 58 ± 12 years) with type 2 diabetes mellitus, hypertension, or obesity. The results of cardiopulmonary exercise testing in patients with structural evidence of SBHF were compared with those in patients with subclinical dysfunction, defined by reduced LV strain ($>-18\%$) or increased LV filling pressure ($E/e' >13$).

RESULTS Compared with healthy subjects, groups with LV abnormalities differed in terms of oxygen uptake (peak VO_2): 25.5 ± 8.2 versus 21.0 ± 8.2 for strain $>-18\%$ ($p < 0.001$); 26.4 ± 8.0 versus 19.0 ± 7.2 for $E/e' >13$ ($p < 0.0001$); and 26.0 ± 7.7 versus 15.9 ± 6.9 ml/kg/min for LVH ($p < 0.0001$). SBHF, defined as ≥ 1 imaging variable present, was associated with lower peak VO_2 (beta = -0.20 ; $p < 0.0001$) and metabolic equivalents (beta = -0.21 ; $p < 0.0001$), independent of higher body mass index and insulin resistance, older age, male sex, and treatment with beta-blockers.

CONCLUSIONS LVH, elevated LV filling pressure, and abnormal myocardial deformation were independently associated with impaired exercise capacity. Including functional markers may improve identification of SBHF in nonischemic heart disease. (J Am Coll Cardiol 2015;■:■-■) © 2014 by the American College of Cardiology Foundation.

Despite remarkable advances, heart failure (HF) remains a major public health problem with an ongoing increase in prevalence (1-3). The progressive nature of HF is reflected in the American College of Cardiology/American Heart Association guidelines, which stratify the disease into 4 stages, differing in terms of cardiac involvement, clinical manifestations, and refractoriness to treatment (4,5). Asymptomatic patients with HF risk factors (including hypertension, type 2 diabetes mellitus [T2DM], and obesity) have stage A heart failure (SAHF). Patients with stage B heart failure (SBHF) have asymptomatic left ventricular (LV) damage, a

greater likelihood for developing overt HF, and specific treatment implications. The frequency of subclinical HF may exceed 50% in community members >45 years of age (6); therefore, early recognition of SBHF offers the potential of altering disease progression therapeutically (7).

The early stages of ischemic HF are more often complicated by LV structural and functional remodeling than nonischemic etiologies, which seem to be marked by more functional than structural changes (8-12). The exclusive reliance on the presence of left ventricular hypertrophy (LVH) and/or reduced left ventricular ejection fraction (LVEF) to ascertain SBHF

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**ABBREVIATIONS
AND ACRONYMS****BNP** = B-type natriuretic peptide**BP** = blood pressure**CAD** = coronary artery disease**cIB** = calibrated integrated backscatter**HF** = heart failure**LV** = left ventricular**LVEF** = left ventricular ejection fraction**LVH** = left ventricular hypertrophy**LVMI** = left ventricular mass index**MET** = metabolic equivalent**SAHF** = stage A heart failure**SBHF** = stage B heart failure**T2DM** = type 2 diabetes mellitus**VO₂** = oxygen uptake

may be insufficient to detect the early stages of nonischemic HF. In this study, we compared the association of LVH and systolic/diastolic dysfunction with exercise capacity, a widely accepted prognostic correlate and marker of disease severity. Our hypothesis was that functional markers (systolic and diastolic dysfunction) would have a similar association with exercise capacity as the structural marker LVH in patients in the asymptomatic stages of HF due to T2DM, hypertension, or obesity.

METHODS

PATIENTS. We prospectively recruited 510 asymptomatic patients with T2DM, obesity, or hypertension from the hospital clinic and community of 2 tertiary medical centers (Princess Alexandra Hospital in Brisbane, Australia [n = 223] and the University Hospital in Wrocław, Poland [n = 287]). Obesity was defined as body mass index ≥ 30 kg/m².

Hypertension was defined as systolic blood pressure (BP) ≥ 140 mm Hg; diastolic BP ≥ 90 mm Hg in at least 2 properly measured, seated BP readings on each of ≥ 2 office visits; or patient on antihypertensive therapy. T2DM was diagnosed according to standard criteria (plasma glucose level, either fasting or 2-h value in 75-g oral glucose tolerance test, or glycated hemoglobin A1c [HbA_{1c}] value).

Participants confirmed their ability to perform physical activity without dyspnea or fatigue. We excluded patients with documented microvascular or macrovascular complications of diabetes, moderate or severe valvular heart disease, congenital heart disease, other significant comorbidities (including malignancy), renal failure, significant psychiatric illness, or absence of stable sinus rhythm. All patients underwent stress echocardiography and were excluded if they had either a history of ischemic heart disease or positive stress testing.

The study complied with the Declaration of Helsinki, and study approval was granted by the human research ethics committees at both institutions. All patients provided informed consent.

DEMOGRAPHIC, ANTHROPOMETRIC, AND METABOLIC DATA. Clinical data were collected regarding patient age, sex, and anthropometry (height, body weight, and hip and waist circumferences). Serum glucose level, insulin level, HbA_{1c} value, creatinine level, and lipid profile were obtained after 12-h fasting and before administration of hypoglycemic agents. Insulin resistance was determined by the homeostasis

model assessment for patients not on supplemental exogenous insulin therapy, calculated as the product of fasting insulin level multiplied by fasting glucose level divided by 22.5.

HEMODYNAMIC DATA AND EXERCISE CAPACITY.

Hemodynamic parameters including heart rate and systolic and diastolic BPs were measured at baseline and at peak exercise. Tonometric pulse wave velocity (SphygmoCor, AtCor Medical, Sydney, Australia) between carotid and femoral sites was used to determine aortic stiffness.

Exercise testing was performed on a treadmill using the Bruce protocol and standard cardiopulmonary stress equipment. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously, and peak oxygen uptake (peak VO₂) was calculated as the average oxygen consumption during the last 30 s of exercise. Exercise capacity was also estimated in metabolic equivalents (METs) based on peak exercise intensity.

ECHOCARDIOGRAPHY. Standard commercially available cardiac ultrasound machines (Vivid 7 and Vivid E9, General Electric Medical Systems, Milwaukee, Wisconsin) were used to perform resting echocardiograms. Images were saved in raw data format for offline analysis to assess LV wall thickness, valvular morphology, and chamber volumes. LV mass was measured using standard criteria and normalized for body size (body surface area or height to the power of 2.7) to obtain left ventricular mass index (LVMI) (13). LVH was determined according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography (14). The modified Simpson biplane method was used to measure LVEF.

Pulsed wave Doppler recordings of LV inflow were acquired from the apical 4-chamber view with the sample volume placed between the tips of the mitral leaflets. Peak early (E) and late diastolic flow velocities (A), ratio of peak early and late diastolic flow velocities (E/A), and deceleration time of early diastolic flow wave were assessed.

Pulsed wave tissue Doppler was performed to establish peak early diastolic mitral annular velocity (e'). The ratio of mitral inflow early diastolic velocity to the average e' velocity obtained from the septal and lateral sides of the mitral annulus (E/e') was calculated to estimate LV filling pressure, and a value >13 was considered to reflect LV filling pressure elevation (15).

Conventional apical views (4-chamber, 2-chamber, and long-axis) in color tissue Doppler format were used to obtain tissue velocity, strain, and strain rate

curves with standard commercial software (EchoPAC, General Electric Vingmed, Wauwatosa, Wisconsin). The image sector angle and optimal depth of imaging were adjusted to achieve a maximal frame rate. Pulse repetition frequency was set at the lowest value without aliasing. The ultrasonic beam was aligned with the myocardial segment of interest to give an insonation angle of $<20^\circ$. The sampling window was located in the center of each segment and tracked manually to keep a fixed midmyocardial position throughout the cardiac cycle.

Peak early diastolic tissue velocity (E_m) was measured in the 6 basal segments, and the resultant values were then averaged to determine mean basal longitudinal E_m , a prognostically important marker of LV relaxation. Parameters assessed from myocardial deformation curves—peak strain, defined as the greatest negative value on the strain curve, and peak systolic and peak early diastolic strain rate—were averaged from all segments measured. Global LV strain of $>-18\%$ was considered abnormal (16,17). Calibrated integrated backscatter (cIB) involved measuring the tissue intensity of the pericardium, posterior wall, and anteroseptum in a parasternal long-axis view and then subtracting the mean pericardial IB intensity at end-diastole from mean IB intensity of the posterior wall and the anteroseptum, which were then averaged to establish mean cIB. All strain, strain rate, myocardial velocity, and integrated backscatter profiles were averaged over 3 consecutive cardiac cycles.

Structural evidence of SBHF required at least moderate LVH ($LVMI \geq 109 \text{ g/m}^2$ in women or $\geq 132 \text{ g/m}^2$ in men). Evidence of functional impairment was defined by $E/e' > 13$ and/or global longitudinal strain of $>-18\%$. **STATISTICAL ANALYSIS.** Sample size was calculated on the basis of our previous work with patients having a similar clinical profile (18). We used longitudinal strain, which was a parameter requiring the highest number of patients to show the significance of differences in exercise capacity, as assessed by peak VO_2 , between groups distinguished by using the pre-specified cut point (18%). Assuming a significant intergroup difference in peak VO_2 of 10%, an SD of 34%, and proportions of patients with strain of $\leq -18\%$ and $>-18\%$ to be 2:1, the predicted sample size was 508 at 90% power and a 2-sided alpha level of 0.05.

Data are presented as mean \pm SD 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 Scheffe post-hoc test for continuous variables or by chi-square test for categorical variables. We used the

Levene test to study homogeneity of variances. Associations between variables were evaluated by Pearson correlation coefficient and stepwise multiple regression analysis. Skewed variables were log-transformed

TABLE 1 Clinical, Metabolic, and Hemodynamic Characteristics in Stage A and B HF

	Stage A (n = 267)	Stage B* (n = 243)	p Value
Demographic and anthropometric characteristics			
Age, yrs	56 \pm 12	60 \pm 12	0.0006
Male	118 (44)	90 (37)	0.11
BMI, kg/m ²	32 \pm 6	33 \pm 5	0.08
Waist circumference, cm	105 \pm 14	105 \pm 13	0.55
Waist-to-hip circumference	0.95 \pm 0.10	0.95 \pm 0.10	0.59
Hypertension	139 (52)	144 (59)	0.11
Diabetes	186 (70)	106 (44)	0.001
Obesity	170 (64)	182 (75)	0.007
LVH by ECG	0 (0)	38 (16)	<0.0001
Biochemistry			
HbA _{1c} , %	7.0 \pm 1.6	7.0 \pm 1.4	0.99
Fasting glucose, mmol/l	7.2 \pm 2.7	6.5 \pm 2.0	0.002
Insulin resistance, log HOMA-IR	0.41 \pm 0.36	0.47 \pm 0.27	0.08
Total cholesterol, mg/dl	191 \pm 47	191 \pm 45	0.88
Low-density lipoprotein, mg/dl	115 \pm 40	113 \pm 39	0.48
High-density lipoprotein, mg/dl	47 \pm 13	47 \pm 13	0.63
Triglycerides, mg/dl	154 \pm 119	160 \pm 77	0.49
Hemoglobin, g/l	143 \pm 13	137 \pm 13	0.0004
Serum creatinine, mg/dl	0.85 \pm 0.20	0.91 \pm 0.24	0.007
Log BNP, pg/ml	3.33 \pm 0.44	3.65 \pm 0.94	0.001
Hemodynamics			
Resting heart rate, beats/min	73 \pm 13	73 \pm 11	0.64
Resting systolic BP, mm Hg	136 \pm 19	137 \pm 15	0.40
Resting diastolic BP, mm Hg	81 \pm 10	80 \pm 8	0.45
Aortic pulse wave velocity, m/s	9.2 \pm 2.2	9.9 \pm 2.4	0.06
Peak heart rate, beats/min	157 \pm 22	139 \pm 22	<0.0001
Peak systolic BP, mm Hg	190 \pm 26	179 \pm 31	0.002
Peak diastolic BP, mm Hg	85 \pm 12	78 \pm 16	<0.0001
Exercise capacity			
METs	9.8 \pm 3.4	6.6 \pm 3.1	<0.0001
Peak VO_2 , ml/kg/min	27.6 \pm 7.3	20.2 \pm 8.0	<0.0001
Medications			
Antihypertensive therapy			
ACEI or ARB	125 (47)	134 (55)	0.06
Beta-blocker	38 (14)	87 (36)	0.001
Calcium channel blocker	24 (9)	51 (21)	0.001
Aldosterone antagonist	2 (1)	0 (0)	0.18
Diuretic	34 (13)	58 (24)	0.002
Statin	102 (38%)	112 (46)	0.07
Hypoglycemic therapy			
Metformin	118 (44)	75 (31)	0.002
Sulphonylurea	58 (22)	38 (16)	0.08
Insulin	29 (11)	13 (5)	0.03
Thiazolidinedione	4 (2)	5 (2)	0.63

Values are mean \pm SD or n (%). *Stage B: global longitudinal strain $>-18\%$, E/e' ratio >13 , or moderate to severe LVH (LV mass index $\geq 109 \text{ g/m}^2$ in women and $\geq 132 \text{ g/m}^2$ in men). LVH by ECG was evaluated using the Sokolow-Lyon criteria.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; ECG = electrocardiogram; HbA_{1c} = glycated hemoglobin A_{1c}; HF = heart failure; HOMA-IR = homeostasis model assessment—insulin resistance; LV = left ventricular; LVH = left ventricular hypertrophy; MET = metabolic equivalent; VO_2 = oxygen uptake.

before being analyzed. A receiver-operating characteristic (ROC) analysis was used to examine the ability of particular variables to predict SBHF. Differences in the area under the ROC curves were analyzed using the z test. The reproducibility of echocardiographic measurements was evaluated by the Bland-Altman method (mean difference and 95% confidence interval). All calculations were carried out with standard statistical software (Statistica for Windows 10, StatSoft Inc., Tulsa, Oklahoma). A p value <0.05 was deemed to be statistically significant.

RESULTS

PATIENT SELECTION. The clinical profile of the studied population included hypertension in 283 patients (55%), T2DM in 292 patients (57%), and obesity in 352 patients (69%). SBHF was identified on the basis of either functional or structural markers in 243 patients (48%), and the rest were considered to have SAHF.

CLINICAL, METABOLIC, AND HEMODYNAMIC FEATURES.

SBHF was characterized by older age; higher prevalence of obesity; higher creatinine and B-type natriuretic peptide (BNP) and lower hemoglobin levels; higher number of prescriptions for beta-blockers, calcium antagonists, and diuretics; and lower exercise capacity and exercise-induced increase in heart rate and BP, compared with SAHF. The frequency of diabetes, hypoglycemic treatment (e.g., metformin, insulin), and fasting glucose levels were higher in SAHF (Table 1).

CARDIAC MORPHOLOGY AND FUNCTION. As expected from the diagnostic criteria, LV structural and functional remodeling in SBHF was evidenced by higher LV end-diastolic dimension, LVMI, and E/e' and lower peak early diastolic myocardial velocity, strain, and strain rate. However, despite the existence of LV impairment by definition in SBHF, LVEF was higher in this subgroup, although the absolute difference between stages A and B was minimal (Table 2).

DISCRIMINATORY VALUES OF LVH, E/E', AND STRAIN. The studied population was stratified using the pre-specified cut points identifying reduced strain (>−18%), increased LV filling pressure (E/e' >13), and moderate LVH (LVMI ≥109 g/m² in women and ≥132 g/m² in men). The Central Illustration demonstrates the effectiveness of each component in discriminating lower exercise capacity.

The additive effect of these LV morphological and functional abnormalities on exercise capacity was evidenced by a progressive decrease in peak VO₂ and METs with increasing number of components with abnormal values in individual patients (Figure 1). The

TABLE 2 Myocardial Structural and Functional Characteristics in Stage A and B HF

	Stage A (n = 267)	Stage B (n = 243)	p Value
LV end-diastolic diameter, mm	48.3 ± 4.8	50.9 ± 5.4	<0.0001
LV mass index, g/m ²	86 ± 19	112 ± 25	<0.0001
LV mass index, g/m ^{2.7}	44 ± 11	58 ± 14	<0.0001
Ejection fraction, %	66 ± 6	67 ± 6	0.02
E/A	1.00 ± 0.31	0.98 ± 0.39	0.47
E wave deceleration time, ms	224 ± 51	229 ± 49	0.25
E _m , cm/s	6.7 ± 2.0	5.8 ± 1.5	<0.0001
E/e'	9.3 ± 1.9	12.6 ± 3.9	<0.0001
Strain, %	21.2 ± 2.7	18.7 ± 2.8	<0.0001
Strain rate—systolic, 1/s	1.42 ± 0.24	1.33 ± 0.21	<0.0001
Strain rate—diastolic, 1/s	1.76 ± 0.37	1.55 ± 0.30	<0.0001
Calibrated integrated backscatter, dB	−18.8 ± 5.4	−18.7 ± 5.2	0.90

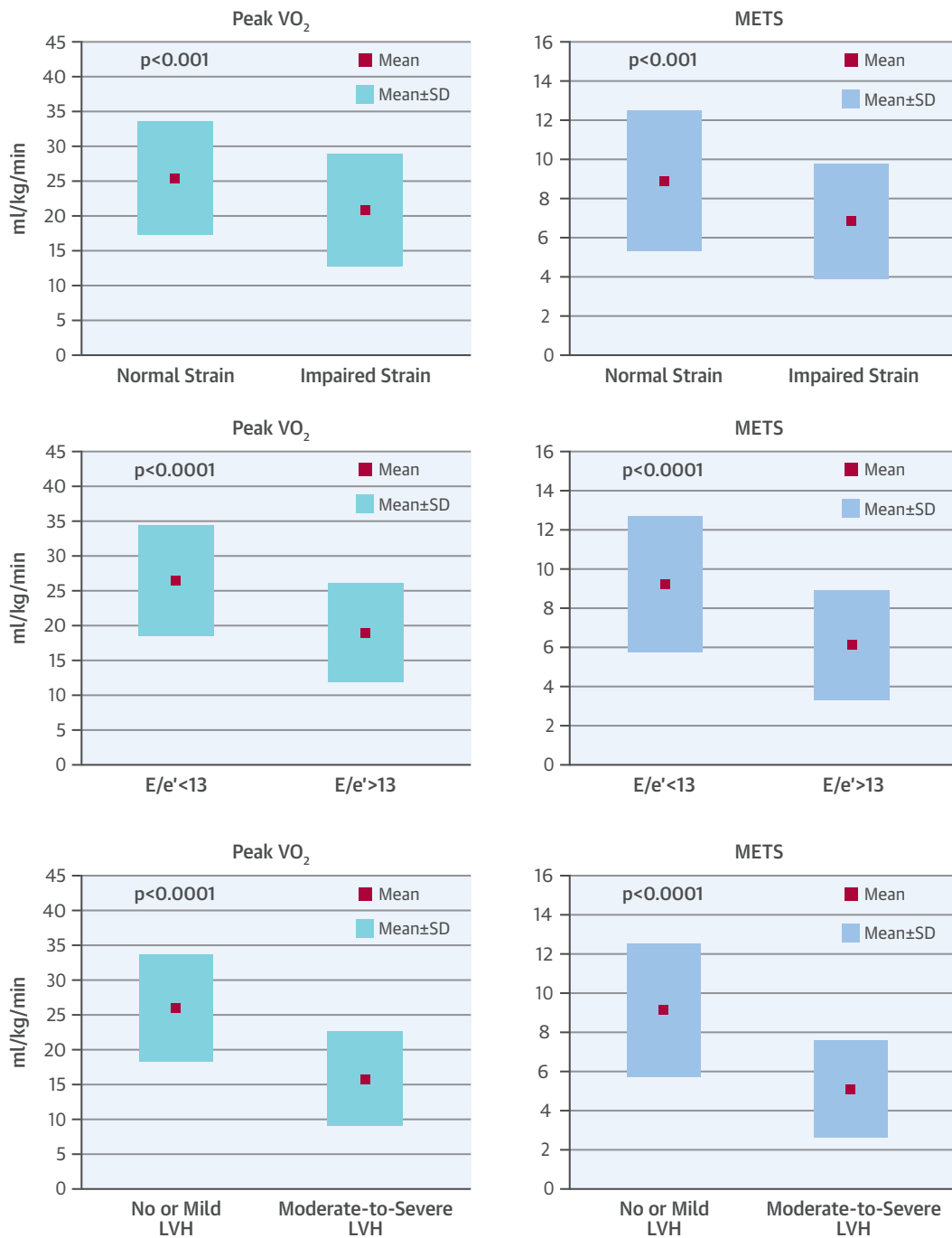
Values are mean ± SD.
E/A = ratio of peak early and late diastolic flow velocities; other abbreviations as in Table 1.

distribution of normal and abnormal values of LV parameters used for the categorization shows that in the group without moderate to severe LVH, E/e' >13 was present in 71 patients (18%) and strain >−18% in 62 patients (16%; 49 in the group with normal E/e' and 13 with abnormal E/e'). This indicates that both LV functional criteria improved recognition of SBHF by identifying patients missed by the LVH criterion alone (Figure 2).

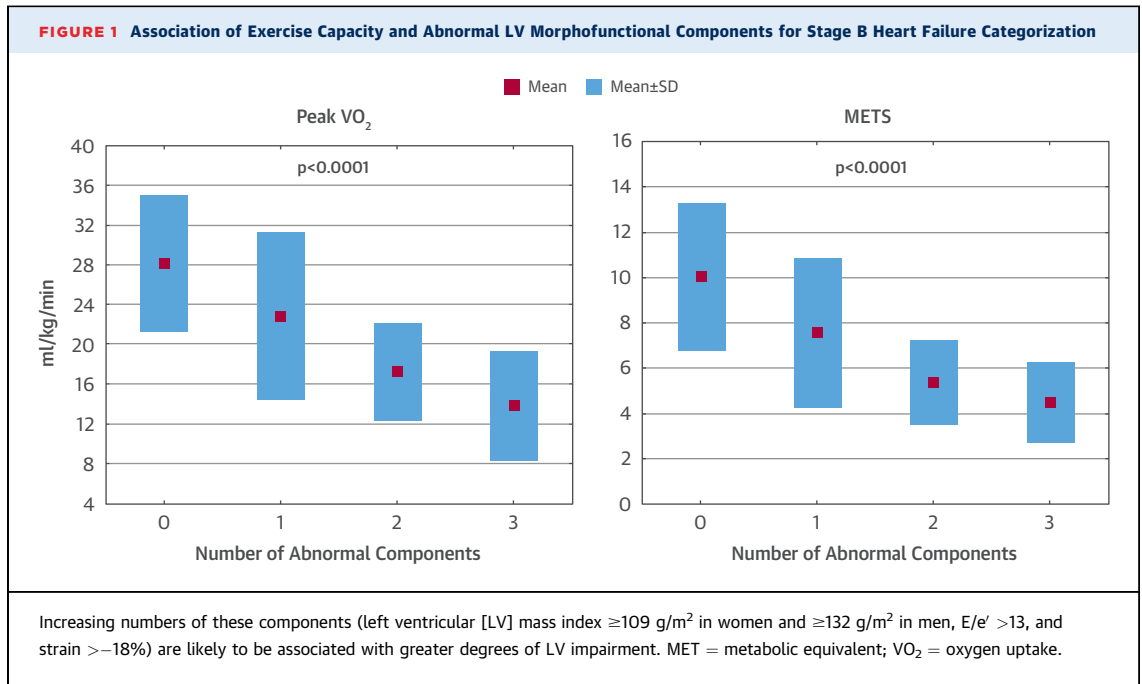
PREDICTIVE SIGNIFICANCE OF EXERCISE CAPACITY, LV ABNORMALITIES, AND BNP. BNP's ability to predict impaired exercise capacity (AUC ± SE 0.61 ± 0.04) was inferior to that of combined LV morphofunctional parameters (0.77 ± 0.03), LVMI (0.79 ± 0.02), E/e' (0.78 ± 0.02), and strain (0.76 ± 0.02) (all p < 0.0001). No differences in the predictive value of LVMI, E/e', and strain for SBHF were found.

PROFILES OF LV ABNORMALITIES AND EXERCISE CAPACITY.

For evaluation of the contribution of different profiles of LV morphofunctional abnormalities to reduced exercise capacity, patients with SBHF were categorized into 3 groups: 1) LVH (LVMI ≥109 g/m² in women and ≥132 g/m² in men); 2) E/e' >13 and no LVH; and 3) global longitudinal strain >−18%, E/e' <13, and no LVH (Table 3). Groups 1 and 2 included older patients and demonstrated lower prevalence of male sex and T2DM. Heart rate and BP at peak exercise were lower in group 1; peak heart rate was reduced in group 2. BNP level progressively increased from group 3 to group 1. LV structural and functional impairment differed across the stage B subgroups depending on the pre-defined

CENTRAL ILLUSTRATION Exercise Capacity According to Different Means of Defining LV Impairment

Both functional markers (including impaired left ventricular [LV] longitudinal deformation and increased filling pressure) and structural markers of LV disease (LV hypertrophy [LVH]) are associated with reduced exercise capacity expressed as oxygen uptake (VO_2) or estimated metabolic equivalents (METS).

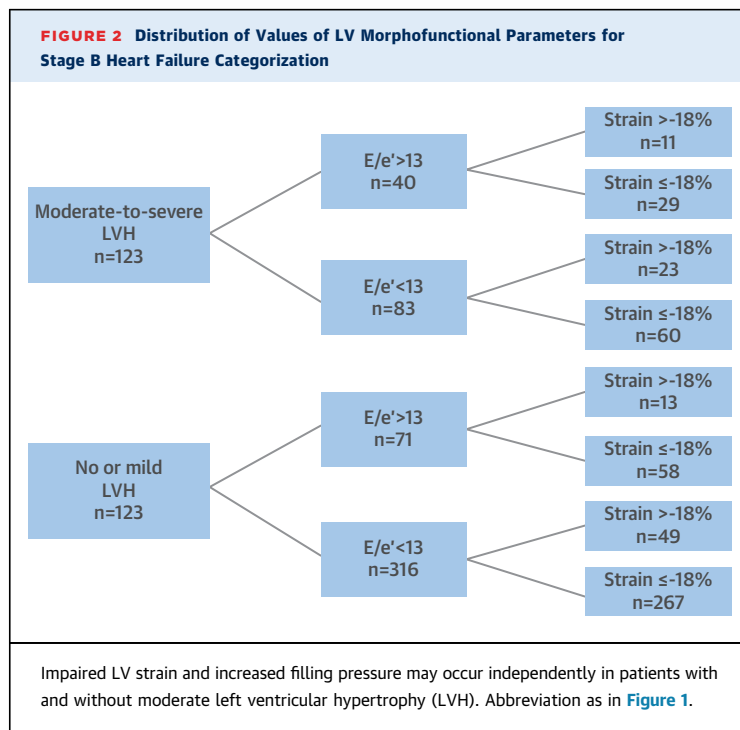


stratification criteria, with LV morphology being the most abnormal in group 1 and LV deformation in group 3. Group 2 presented different degrees of abnormal changes, with diastolic derangement the most profound (Table 4).

Compared with SAHF, exercise capacity was significantly reduced in all 3 SBHF subgroups, as indicated by lower peak VO₂ and METs; group 1 had the most severe impairment (Figure 3).

ASSOCIATIONS. Stepwise multiple regression models were built to determine independent correlations of LV systolic and diastolic function. This analysis showed that, apart from higher body mass index and insulin resistance, older patient age, male sex, and treatment with beta-blockers, the presence of SBHF (based on LVMI, strain, or diastolic changes) was independently associated with lower exercise capacity, as estimated by peak VO₂ and METs (Table 5). The independent effect of LVMI, diastolic dysfunction, and strain on exercise capacity was validated by replacing these covariates within each multivariable model by a categorical variable to reflect LVMI, E/e', and strain (for the model with peak VO₂: beta for LVMI -0.13, for E/e' -0.14, and for strain -0.11; all $p < 0.0001$; for the model with METs: beta for LVMI -0.10 [$p < 0.005$], for E/e' -0.14 [$p < 0.0001$], and for strain -0.12 [$p < 0.0005$]). Other variables tested in the multivariable models included BP, waist, waist-to-hip ratio, creatinine level, other pharmacological treatment, coexistence of T2DM and hypertension, aortic pulse wave velocity, and cIB.

Including patients with mild LVH in diagnosing SBHF is potentially problematic because of the limited accuracy of standard echocardiographic techniques for categorizing LVMI in individuals



rather than populations. However, the validity of taking into account LV functional criteria was corroborated after patients with mild LVH were included in the SBHF group (Online Figure 1, Online Table 1).

REPRODUCIBILITY. The reproducibility of myocardial measurements was calculated using values averaged from all the segments subjected to analysis (except for E/e' , which can be calculated only as a global LV parameter) in 15 randomly selected examinations and the intraobserver and interobserver variability (the latter evaluated across sites) (Table 6).

DISCUSSION

The evolution from SAHF to SBHF is usually identified based on LV structural abnormalities, which are associated with reduced LV functional reserve even without clear symptoms. Our findings indicated that not only structural (LV mass) but also functional (increased LV filling pressure, abnormal myocardial deformation) parameters contributed to lower exercise capacity in the asymptomatic phase of HF. We propose that not only LVH, but also increased E/e' and/or decreased LV strain, should be considered when identifying SBHF (Central Illustration).

PRECLINICAL HF. Myocardial injury promotes subsequent maladaptive remodeling with deleterious changes in ventricular structure and function, eventually leading to symptomatic HF (1,19–22). Early detection of pre-clinical cardiac abnormalities is a mandatory first step to implementing suitable and effective interventions for HF prevention, including pharmacotherapies and/or behavioral modifications (7). The importance of defining accurate staging criteria is underpinned by clinical data, which have demonstrated that even the progression within the asymptomatic phase of HF (from stage A to stage B) is associated with decreased survival in males, whereas the advent of HF symptoms (stage C) carries a 5-fold increase in the risk of mortality in both sexes (6).

Practically, however, SBHF identification may be problematic in patients with risk factors but with no HF symptoms, no evidence of ischemic heart disease, and normal cardiac size and LVEF. Conventional echocardiographic parameters have not been useful in recognizing SBHF in this setting. Apart from diastolic abnormalities (6), detection of decreased longitudinal deformation, widely recognized as a marker of early myocardial disease (23), might be helpful in the distinction between stages A and B of HF.

EXERCISE CAPACITY. Epidemiological studies have revealed that exercise capacity is a powerful independent predictor of cardiovascular events and

TABLE 3 Clinical, Metabolic, and Hemodynamic Characteristics in Stage A and B HF Stratified by LV Longitudinal Deformation, Filling Pressure, and Hypertrophy

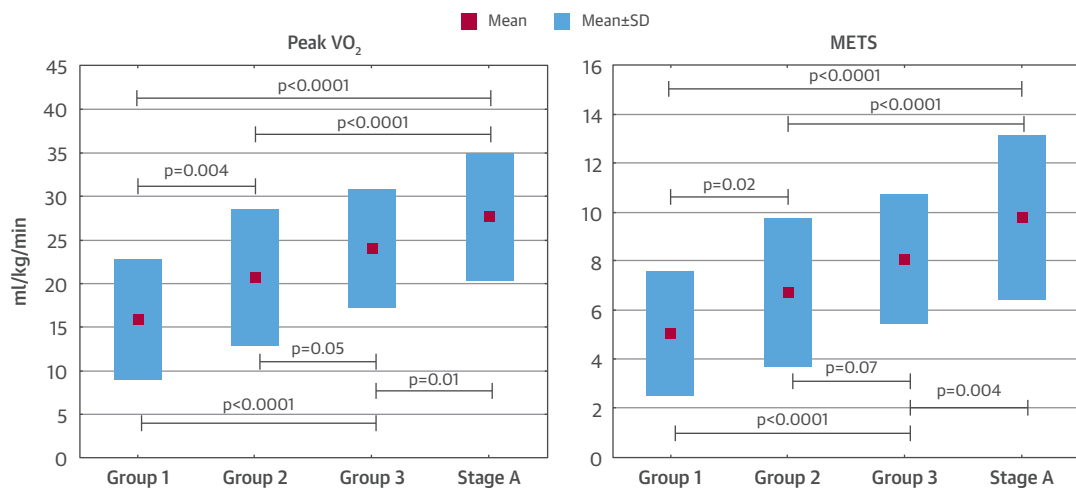
	Group 1* (n = 123)	Group 2† (n = 71)	Group 3‡ (n = 49)	Stage A (n = 267)	p Value
Demographic and anthropometric characteristics					
Age, yrs	61 ± 12§	60 ± 11¶	56 ± 11	56 ± 12	0.001
Male sex	32 (26)§#	28 (39)¶	30 (61)¶	118 (44)	0.001
BMI, kg/m ²	33 ± 5	34 ± 6	34 ± 5	32 ± 6	0.13
Hypertension	77 (63)	41 (58)	24 (49)	139 (52)	0.19
Diabetes	39 (32)§#**	36 (51)§	31 (63)	186 (70)	0.001
Obesity	86 (70)	58 (81)¶	38 (77)	170 (64)	0.02
Biochemistry					
Insulin resistance, log HOMA-IR	0.46 ± 0.29	0.47 ± 0.27	0.52 ± 0.25	0.41 ± 0.36	0.26
Serum creatinine, mg/dl	0.91 ± 0.21	0.90 ± 0.27	0.89 ± 0.25	0.85 ± 0.20	0.06
Log BNP, pg/ml	3.85 ± 1.36§	3.63 ± 0.67¶	3.44 ± 0.72	3.33 ± 0.45	0.001
Hemodynamics					
Resting heart rate, beats/min	71 ± 8	75 ± 11	74 ± 13	73 ± 13	0.20
Resting systolic BP, mm Hg	138 ± 15	137 ± 14	136 ± 17	136 ± 18	0.78
Resting diastolic BP, mm Hg	78 ± 10	80 ± 9	80 ± 10	81 ± 11	0.84
Aortic pulse wave velocity, m/s	10.8 ± 1.4	10.4 ± 2.9	9.2 ± 1.9	9.2 ± 2.2	0.06
Peak heart rate, beats/min	129 ± 18§#	140 ± 20§	154 ± 20	157 ± 22	<0.0001
Peak systolic BP, mm Hg	164 ± 25§#**	182 ± 27	195 ± 33	190 ± 26	<0.0001
Peak diastolic BP, mm Hg	70 ± 12§#**	82 ± 14	84 ± 18	85 ± 12	<0.0001

Values are mean ± SD or n (%). *Group 1: stage B with moderate to severe LVH (LV mass index ≥109 g/m² in women and ≥132 g/m² in men). †Group 2: stage B with $E/e' >13$ and no moderate to severe LVH. ‡Group 3: stage B with global longitudinal strain >−18%, $E/e' <13$, and no moderate to severe LVH. §p < 0.001 versus stage A. ||p < 0.01 versus group 3. ¶p < 0.05 versus stage A. #p < 0.001 versus group 3. **p < 0.01 versus group 2. Abbreviations as in Table 1.

TABLE 4 Myocardial Structural and Functional Characteristics in Stage A and B HF Stratified by LV Longitudinal Deformation, Filling Pressure, and Hypertrophy

	Group 1* (n = 123)	Group 2† (n = 71)	Group 3‡ (n = 49)	Stage A (n = 267)	p Value
LV end-diastolic diameter, mm	52.6 ± 4.7§ ¶	49.3 ± 5.3	48.9 ± 6.0	48.3 ± 4.8	<0.0001
LV mass index, g/m ²	130 ± 16§ ¶	94 ± 19#	94 ± 21#	86 ± 19	<0.0001
LV mass index, g/m ^{2.7}	68 ± 9§	49 ± 11§	48 ± 11#	44 ± 11	<0.0001
Ejection fraction, %	67 ± 6	68 ± 6	66 ± 6	66 ± 6	0.06
E/A	0.96 ± 0.45	1.00 ± 0.30	0.99 ± 0.31	1.00 ± 0.31	0.72
E wave deceleration time, ms	235 ± 48	220 ± 49	227 ± 47	224 ± 51	0.13
E_m , cm/s	5.9 ± 1.6§	5.5 ± 1.4§	6.0 ± 1.7#	6.7 ± 2.0	<0.0001
E/e'	12.4 ± 4.2§ ¶	15.3 ± 2.5§	9.4 ± 1.7	9.3 ± 1.9	<0.0001
Strain, %	18.9 ± 2.5§ ¶	20.0 ± 3.0 #	16.1 ± 1.0§	21.2 ± 2.7	<0.0001
Strain rate—systolic, 1/s	1.37 ± 0.20	1.37 ± 0.19	1.15 ± 0.18§	1.42 ± 0.24	<0.0001
Strain rate—diastolic, 1/s	1.55 ± 0.26§	1.60 ± 0.33§	1.44 ± 0.34§	1.76 ± 0.37	<0.0001
Calibrated integrated backscatter, dB	19.4 ± 5.3	18.2 ± 4.3	17.7 ± 5.8	18.8 ± 5.4	0.17

Values are mean ± SD. *Group 1: stage B with moderate to severe LVH (LV mass index ≥109 g/m² in women and ≥132 g/m² in men). †Group 2: stage B with $E/e' >13$ and no moderate to severe LVH. ‡Group 3: stage B with global longitudinal strain >−18%, $E/e' <13$, and no moderate to severe LVH. §p < 0.001 versus stage A. ||p < 0.001 versus group 3. ¶p < 0.01 versus group 2. #p < 0.05 versus stage A. Abbreviations as in Tables 1 and 2.

FIGURE 3 Exercise Capacity According to Combinations of Impaired LV Measures

The addition of increasing degrees of functional disturbance to moderate LVH is associated with progressive impairment of functional capacity. Group 1: Stage B with moderate to severe LVH (LV mass index ≥ 109 g/m² in women and ≥ 132 g/m² in men). Group 2: Stage B with E/e' >13 and no moderate to severe LVH. Group 3: Stage B with global longitudinal strain $>-18\%$, E/e' <13 , and no moderate to severe LVH. Abbreviations as in [Figures 1 and 2](#).

all-cause mortality among asymptomatic patients, with a relative risk comparable to those of many other established prognosticators (24-26). Impaired LV filling and reduced myocardial deformation, which are both associated with impaired exercise capacity, are common findings in patients with hypertension, T2DM, or obesity, regardless of HF symptoms (8,11,16). The current study demonstrated that, in addition to morphological criteria (LVH), the application of various functional criteria (diastolic

dysfunction with LV filling pressure elevation and reduced longitudinal strain) identified patients with SBHF as a group with impaired exercise capacity in comparison to those with SAHF. Decreased LV longitudinal strain was associated with lower exercise capacity independently of coexisting increased LV mass and advanced diastolic dysfunction. This concept is consistent with the pathophysiological role and prognostic significance of decreased myocardial deformation in HF (27-31).

Multivariable analysis reinforced the strategy of defining SBHF by the presence of moderate LVH and/or diastolic dysfunction with elevated LV filling pressure and/or reduced LV longitudinal strain. This showed that SBHF identified via the new criteria independently predicted lower exercise capacity. This information is incremental to that obtained from clinical and demographic factors such as age, sex, body weight, insulin resistance, and medication use.

TABLE 5 Multivariable Predictors of Exercise Capacity

	Beta	SE	p Value
Peak VO ₂ R ² = 0.83			
Treatment with beta-blockers	-0.38	0.03	0.0001
Male sex	0.41	0.03	0.0001
BMI	-0.40	0.03	0.0001
Age	-0.40	0.03	0.0001
Stage B	-0.20	0.03	0.0001
Log HOMA-IR	-0.10	0.03	0.0009
Hypertension	-0.04	0.03	0.27
METs R ² = 0.78			
Treatment with beta-blockers	-0.38	0.03	0.0001
BMI	-0.40	0.03	0.0001
Age	-0.46	0.03	0.0001
Male sex	0.32	0.03	0.0001
Stage B	-0.21	0.03	0.0001
Log HOMA-IR	-0.08	0.03	0.02

Abbreviations as in [Table 1](#).

TABLE 6 Reproducibility of Myocardial Deformation Parameters

	Intraobserver Variability	Interobserver Variability
Strain, %	0.7 ± 0.4	0.8 ± 0.5
Peak systolic strain rate, /s	0.1 ± 0.1	0.1 ± 0.1
Peak diastolic strain rate, /s	0.2 ± 0.3	0.3 ± 0.3
E/e'	0.5 ± 0.5	0.3 ± 0.7

Values are mean ± SD. Variability is expressed for 2 observations by the same and different observers.

PROGNOSTIC SUPPORT FOR FUNCTIONAL INDEXES.

The lifetime risk of developing overt HF after reaching 40 years of age is as high as 20% (32). Numerous clinical investigations have demonstrated an independent prognostic value of LV diastolic dysfunction for predicting adverse events in various disorders, including ischemic and hypertensive heart disease, end-stage renal disease, and cardiomyopathies (15). The presence of diastolic disturbances potentiates the risk of future HF and hospitalization; the association with mortality is more ambiguous, mainly due to an unknown burden of clinically significant coronary artery disease (CAD) confounding the relationship between diastolic dysfunction and outcomes (33,34). Nonetheless, studies have consistently shown that among the diastolic parameters, E/e' (a proxy for LV filling pressure and hemodynamic marker of diastolic dysfunction) is highly predictive for risk of death and other adverse events regardless of the coexistence of relevant myocardial ischemia (15,34).

Assessment of LV systolic function is an essential method of cardiovascular risk stratification. LVEF, the most commonly used systolic parameter, offers its most effective prognostication in the setting of significant dysfunction; it provides less reliable prognostic information when its values are normal or near normal or LVH coexists (35). Growing evidence, including a recent meta-analysis, indicates that global longitudinal strain may outperform LVEF in predicting adverse cardiac events, irrespective of underlying disease pathology, and the benefit from myocardial deformation evaluation may be particularly evident in patients with relatively preserved systolic performance (28,30,31,35). Thus, available data on the prognostic implications of impaired longitudinal strain and abnormal diastolic function support the inclusion of these functional indexes as SBHF criteria.

Circulating BNP levels also supported our approach of including functional indexes in defining SBHF. In addition to being significantly higher in SBHF, BNP levels correlated with degree of functional impairment. BNP is predictive of mortality and cardiovascular outcomes in asymptomatic patients, with a prognostic threshold lower than that regarded as diagnostic for HF (36). Accordingly, higher BNP values in SBHF might be associated with a higher cardiovascular risk and support using functional indexes when defining SBHF.

STUDY LIMITATIONS. This paper is based on observational data. Our study's cross-sectional character precludes assessing time-dependent changes and conclusions about causal relationships. The estimation of LV diastolic dysfunction severity was based on E/e' , rather than a composite approach, taking into

account other diastolic parameters. This might have contributed to misclassification of some cases with truly increased LV filling pressure but an $E/e' < 13$. Finally, we excluded patients with CAD to avoid the potential impact of myocardial ischemia on exercise capacity, but this may limit the generalizability of our findings to the broader spectrum of cardiac diseases. The absence of CAD could not be definitely ascertained without angiographic verification. However, referral for coronary diagnostic procedures without clear clinical indications was not considered ethically justifiable.

CONCLUSIONS

The high prevalence of asymptomatic stages of HF and their possible progression to clinically overt disease with a negative impact on prognosis should increase diagnostic and treatment efforts for HF prevention. The inclusion of LV deformation and filling pressure expands the array of echocardiographic measures used for SBHF discrimination by adding major aspects of early myocardial impairment. The increasing potential of commercially available equipment for myocardial strain analysis extends the possibility of improving the recognition of SBHF at only a slight increase in duration of echo examination and overall cost of diagnostic procedures.

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PERSPECTIVES**CLINICAL COMPETENCY IN MEDICAL KNOWLEDGE:**

Stage B heart failure constitutes a pre-clinical phase of heart failure, associated with risk of progression to heart failure and death.

CLINICAL COMPETENCY IN PATIENT CARE: The definition of this entity is currently based around structural perturbations.

TRANSLATIONAL OUTLOOK 1: Left ventricular function disturbances are readily apparent using echocardiographic measures. This prognostically valuable information is associated with exercise capacity.

TRANSLATIONAL OUTLOOK 2: Reporting of both strain and diastolic dysfunction may be of value in recognition of the pre-clinical phases of nonischemic heart failure.

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KEY WORDS exercise capacity, diastolic dysfunction, strain

APPENDIX For a supplemental table and figure, please see the online version of this article.