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CLINICAL RESEARCH

Determinants of Effort Intolerance in Patients With Heart Failure

Combined Echocardiography and Cardiopulmonary Stress Protocol

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ABSTRACT

OBJECTIVES The purpose of this study was to assess individual mechanisms of effort intolerance in patients with heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), or normal cardiac function using combined echocardiography and cardiopulmonary stress testing.

BACKGROUND Combined stress echocardiography and cardiopulmonary tests visualize cardiac chambers in 4 well-defined activity levels (rest, unloaded, anaerobic threshold, and peak), allowing noninvasive assessment of cardiac function, hemodynamics, and arterial venous oxygen content difference (AVo_2Diff) during all stages.

METHODS Left ventricular volumes, stroke volume (SV), S', E/e', oxygen consumption (Vo_2), and AVo_2Diff were measured in all effort stages using ramp semirecumbent cycle prolonged (≥8 min) exercise in 45 consecutive subjects evaluated for effort intolerance (14 normal cardiac function, 16 HFpEF, and 15 HFrEF patients; age 56.5 ± 16 years; 73% male).

RESULTS In HFpEF and HFrEF, the changes in Vo_2 were attenuated (between group $p = 0.003$; group by time interaction $p < 0.0001$), as well as peak heart rate ($p = 0.0001$; $p = 0.0001$) and SV ($p = 0.006$; $p = 0.0001$). End-diastolic volume to E/e' ratio (measure of compliance) was superior in HFrEF and normal patients at baseline but worsened in HFpEF and HFrEF at peak exercise (8.3 ± 4 vs. 11.6 ± 5 vs. 19.1 ± 8; $p = 0.004$; $p = 0.01$). Functional mitral regurgitation worsened even during the unloaded stage, mostly in patients with HFrEF, but also in several patients with HFpEF. In multivariable analysis, heart rate response ($p = 0.007$), and AVo_2Diff ($p < 0.0001$) were the most significant independent predictors of effort capacity; SV was not.

CONCLUSIONS Combined tests are feasible and allow noninvasive evaluation of effort intolerance. In HFpEF and HFrEF patients, exercise intolerance is predominantly due to chronotropic incompetence and peripheral factors. Combined stress echocardiography and cardiopulmonary tests may have potential for clinical management and selection of patients for trials. (J Am Coll Cardiol HF 2015;3:803–14) © 2015 by the American College of Cardiology Foundation.

Multiple mechanisms are held responsible for the limited exercise capacity of patients with heart failure (HF) with preserved (HFpEF) or reduced (HFrEF) left ventricular (LV) ejection fraction (EF) (1-8). Studies of exercise limitation in HF have predominantly used standard exercise tests or radionuclide ventriculography combined with invasive hemodynamic assessment.

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ABBREVIATIONS AND ACRONYMS

AVo_2Diff = arterial venous oxygen content difference

CPET = cardiopulmonary exercise test

EF = ejection fraction

FEV_1 = forced expiratory volume first second

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LV = left ventricle

LVEDV = left ventricular end-diastolic volume

MR = mitral regurgitation

SE = stress echocardiography

SV = stroke volume

Vco_2 = carbon dioxide production

Vo_2 = oxygen consumption

They have been limited by their invasive nature, resulting in selection bias, and by the insufficient anatomic data provided with ventriculography (1,5). Several studies have used stress echocardiography (SE) to assess factors limiting maximal exercise capacity by comparing rest to peak exercise (2,9,10).

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Because HF patients rarely exercise at maximal intensities, and submaximal exercise capacity is more applicable to everyday life, it is particularly important to expand the understanding of cardiac peripheral and vascular responses to submaximal exercise in this population. Cardiopulmonary exercise tests (CPET) are able to recognize and divide effort into 4 activity levels (rest, unloaded cycling, anaerobic threshold, and peak), allowing assessment of cardiac function during all exercise levels. Therefore, we have created a new combined cardiopulmonary stress test and SE protocol enabling the noninvasive assessment of multiple cardiac and peripheral responses to dynamic exercise, in all 4 predefined activity levels.

METHODS

STUDY POPULATION. Between January 1, 2013 and September 30, 2013, we performed 72 combined CPET and SE examinations using our new protocol. All patients were clinically stable and ambulatory, and referred for evaluation of effort intolerance or dyspnea. Patients presenting with primary valvular disease (aortic valve replacement, n = 2; aortic stenosis, n = 2; rheumatic mitral stenosis, n = 4; organic mitral regurgitation [MR], n = 1), hypertrophic cardiomyopathy (n = 6), sinoatrial block (n = 1), active ischemia (n = 2), atrial septal defect (n = 1), primary pulmonary hypertension (n = 1), mitochondrial myopathy (n = 1), unable to complete exercise on semirecumbent bicycle (respiratory exchange ratio <1.0; n = 4), or with inadequate acoustic windows (n = 2) were excluded from the study. The remaining patients were divided into 3 groups (controls, HFpEF, and HFrEF). Control patients were clinical patients referred to the test for dyspnea of unknown origin. Eight patients were concluded to have effort dyspnea related to peripheral factors based on normal LV, right ventricle systolic and diastolic function, and impaired oxygen extraction in peripheral muscles. The remaining 7 patients had normal exercise capacity. Diagnosis of HFpEF and HFrEF was made clinically before the test based on clinical signs and symptoms of HF as defined by the criteria of Rich et al. (11). Patients were defined to have HFpEF when they had a normal resting EF (≥50%), or HFrEF when they had a low resting EF (<50%) (**Table 1**).

EXERCISE PROTOCOL. A symptom-limited graded ramp bicycle exercise test was performed in the semisupine position on a tilting, dedicated, microprocessor-controlled eddy current brake stress echocardiography cycle ergo meter (Ergoselect 1000 L, CareFusion, San Diego, California). We estimated the expected peak oxygen consumption (Vo_2) based on patient age, height, and weight after considering the patient's history. We then calculated the work rate increment necessary to reach the patient's estimated peak Vo_2 in 8 to 12 min. The protocol included 3 min of unloaded pedaling, a symptom-limited ramp-graded exercise, and 2 min of recovery. Breath-by-breath minute ventilation, carbon dioxide production (Vco_2), and oxygen consumption (Vo_2) were measured using a Medical Graphics metabolic cart (ZAN, nSpire Health Inc., Longmont, Colorado). Peak Vo_2 was the highest averaged 30-s Vo_2 during exercise (12). Ventilation/Vco_2 was defined as the lowest immediately after anaerobic threshold, and was expressed as absolute nadir ventilation/Vco_2 (12,13). Anaerobic threshold was determined manually using the modified V-slope method (13). A 12-lead electrocardiograph and noninvasive arterial saturation were monitored continuously; heart rate and blood pressure were measured at rest and every minute during exercise. β-Blockers and calcium blockers were left unchanged. The metabolic-chronotropic relationship was calculated from the ratio of the HR reserve to the metabolic reserve during submaximal exercise. A metabolic-chronotropic relationship slope of <0.80 was considered indicative of chronotropic incompetence (14,15). In patients on β-blocker or calcium blocker therapy, chronotropic incompetence was defined whenever <62% of heart rate reserve was used (16).

EXERCISE ECHOCARDIOGRAPHY TESTING. Echocardiographic images were obtained concurrently with breath-by-breath gas exchange measurements, at rest, during the 3-min period of unloaded exercise, immediately after reaching the anaerobic threshold, and at maximal exercise capacity, defined as immediately after reaching a respiratory exchange ratio of >1.05. Data collected at each time period included left ventricular end-diastolic volume (LVEDV), end-systolic volume, EF, stroke volume (SV), peak E-wave and A-wave velocities, E-wave

deceleration time, and e′ in the septal mitral annulus. LVEDV, end-systolic volume, and EF were calculated based on the single plane ellipsoid apical 4-chamber area-length method (17). SV was calculated by multiplying the LV outflow tract area at rest by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler during each activity level. The E/e' ratio was calculated at all effort stages. During sinus tachycardia whenever merging of mitral E-wave and A-wave velocities occurred, peak E-wave velocity, E-wave deceleration time, A-wave velocity, e', and E/e' ratio were measured by the methods used by Nagueh et al. (18). Valvular regurgitation was qualitatively assessed using color Doppler at each stage of stress. Whenever regurgitation was more than mild, it was quantified using the continuity method. The arterial venous oxygen content difference (AVo_2Diff) was calculated by using the Fick equation as: Vo_2/echocardiography calculated cardiac output at each activity level (17). Systemic vascular resistance was calculated as mean arterial pressure ([cuff systolic + cuff diastolic blood pressurex2]/3) divided by echocardiography calculated cardiac output and multiplied by 80 during each activity level.

STATISTICAL ANALYSIS. Descriptive results were expressed as mean ± SD for continuous variables and as percentages for categorical variables. For analysis of differences in echocardiography and exercise variables between the HFpEF, HFrEF, and normal controls, we used analysis of variance for continuous, normally distributed variables, the Wilcoxon test for other continuous variable, and Fisher exact test or chi-square tests for categorical variables. Multiple comparisons for continuous and categorical parameters between group pairs used the Tukey-Kramer test for continuous and the Bonferroni correction for categorical variables, respectively. To analyze the differences in the different stages of effort, we compared each stress parameter with the same parameter in the following phase in the effort cycle by paired *t* test using stringent levels of significance ($p < 0.01$ and $p < 0.001$) to minimize false-positive results. We used the repeated measures linear model analysis to define the within-group effect for each parameter over time, the between-group differences over time, and the group-by-time interactions. To analyze the determinants of exercise tolerance, the primary endpoint was peak Vo_2. Univariate analysis to assess association of rest and effort (at each stage) parameter and peak Vo_2 was performed in the first step. In the second step, we used stepwise multivariate linear regression models (with the peak Vo_2 as the dependent variable and the echocardiography and cardiopulmonary stress variables as independent variables) for each effort stage individually. Variables assessing rest echocardiography parameters were entered first in all models, and effort echocardiography parameters (unloaded/anaerobic threshold/peak exercise) were added consecutively to the models. The entry criterion was a univariate $p < 0.1$. To detect collinearity, we used correlation factor analyses to determine whether any pairs of predictor variables were correlated (correlation coefficients over 0.9). If any such pairs were found, the variable with the lowest univariate p value was chosen to be included in the analysis. We performed a separate multivariate linear regression model in each subgroup of patients to evaluate the relative contributions of the peak exercise variables to peak Vo_2. All computations were performed using JMP statistical software for Windows (version 9.0, SAS Institute Inc., Cary, North Carolina).

RESULTS

ECHOCARDIOGRAPHY AND STRESS CORRELATES OF EXERCISE CAPACITY. Clinical, baseline, anaerobic threshold, and maximal CPET characteristics of the HFpEF, HFrEF, and controls are shown in **Table 2** and **Figure 1**. Individual cases are shown in Online Figures 1A, 1B, and 2.

PERIPHERAL OXYGEN EXTRACTION AND LV COMPLIANCE. In HFpEF patients, AVo_2Diff increased normally throughout exercise, but E/e' was higher in all effort stages, resulting in reduced ratio of end-diastolic volume to E/e' (LVEDV/E/e' ratio; low compliance). In HFrEF patients, AVo_2Diff reached plateau at the anaerobic threshold without further increase in the end part of exercise. Although the LVEDV/E/e' ratio was normal at baseline, it decreased during exercise, in marked difference to controls, and HFpEF patients, who had low compliance all the way through exercise.

UNIVARIATE AND MULTIVARIABLE ANALYSES. The results of univariate analysis to assess associations between rest and stress echocardiography parameters with peak Vo_2 are shown in **Table 3**. The only rest echocardiography parameters associated with effort capacity were related to increased left filling pressure, or longitudinal contraction. Multiple stress parameters were associated with peak Vo_2, even when measured very early during the effort cascade.

Stepwise multivariable analyses to explore the independent determinants of peak Vo_2 are shown in

TABLE 1 Participant Characteristics

	Controls (n = 14)	HFpEF (n = 16)	HFrEF (n = 15)	All	p Value: Control vs. HFpEF	p Value: Control vs. HFrEF	p Value: HFpEF vs. HFrEF
Clinical							
Age, yrs	50.9 ± 4.0	57.2 ± 4.0	61.0 ± 4.0	0.20	NS	NS	NS
Male	9 (60)	14 (93)	10 (67)	0.06	NS	NS	NS
Height, m	1.7 ± 0.03	1.7 ± 0.03	1.7 ± 0.03	0.60	NS	NS	NS
Weight, kg	77.2 ± 3.9	79.0 ± 3.9	79.2 ± 3.9	0.90	NS	NS	NS
Body mass index	27.0 ± 1.3	26.6 ± 1.3	28.4 ± 1.3	0.60	NS	NS	NS
Body surface area	1.87 ± 0.06	1.91 ± 0.06	1.95 ± 0.05	0.60	NS	NS	NS
Hypertension	2 (13)	7 (46)	10 (66)	0.02	0.05	0.007	NS
Diabetes mellitus	2 (13)	9 (60)	4 (27)	0.04	0.01	NS	NS
Hyperlipidemia	3 (20)	7 (46)	9 (60)	0.02	0.05	0.007	NS
Creatinine, mg/dl	1.08 ± 0.1	1.19 ± 0.3	1.55 ± 0.1	0.02	NS	0.01	NS
Hemoglobin, g/dl	13.9 ± 0.4	13.1 ± 0.4	13.0 ± 0.5	0.30	NS	NS	NS
CABG	0 (0)	1 (6)	2 (13)	0.20	NS	NS	NS
Charlson score	0 [0, 0.5]	1 [0, 1.75]	2 [0, 3.0]	0.03	NS	0.03	NS
Aspirin	7 (46)	8 (53)	8 (53)	0.70	NS	NS	NS
β-Blockers	4 (26)	9 (60)	11 (73)	0.03	0.009	0.05	NS
Furosemide	0 (0)	6 (40)	10 (67)	<0.0001	0.006	<0.0001	NS
Systolic blood pressure, mm Hg	120.3 ± 45.0	136.6 ± 43.0	117 ± 27	0.40	NS	NS	NS
Diastolic blood pressure, mm Hg	72.1 ± 25.0	70.2 ± 29.0	65.1 ± 25.0	0.80	NS	NS	NS
Echocardiography							
Ejection fraction	64.7 ± 7.0	66.6 ± 6.9	38.9 ± 12.5	<0.0001	NS	<0.0001	<0.0001
Diastolic dimension, mm	47.8 ± 3.9	45.7 ± 4.3	60.9 ± 7.8	<0.0001	NS	<0.0001	<0.0001
Systolic dimension, mm	30.3 ± 4.0	28.7 ± 4.0	49.6 ± 10.4	<0.0001	NS	<0.0001	<0.0001
End-diastolic volume, ml	123 ± 20	122 ± 18	201 ± 59	<0.0001	NS	<0.0001	<0.0001
End-diastolic volume index, ml/m^2	66.4 ± 12.0	65.1 ± 13.0	103.2 ± 28	<0.0001	NS	<0.0001	<0.0001
End-systolic volume, ml	44 ± 13	41 ± 11	127 ± 56	<0.0001	NS	<0.0001	<0.0001
End-systolic volume index, ml/m^2	23.7 ± 8.0	21.8 ± 6.0	64.9 ± 27.0	<0.0001	NS	<0.0001	<0.0001
LV mass index, g/m^2	94.6 ± 31.0	124.9 ± 39.0	126 ± 41	0.04	0.045	0.04	NS
Relative wall thickness	0.41 ± 0.07	0.54 ± 0.12	0.31 ± 0.08	<0.0001	0.001	0.009	0.001
LAVI, ml/m^2	22.1 ± 6.9	37.4 ± 13.3	44.1 ± 19.8	0.0004	0.01	0.004	NS
Stroke volume, ml/beat	77.3 ± 10.0	78.8 ± 17.0	67.1 ± 20.0	0.11	NS	NS	NS
Cardiac output, l/min	6.2 ± 1.1	6.0 ± 1.5	4.9 ± 1.5	0.03	NS	0.03	NS
Cardiac index, l/min/m^2	3.3 ± 0.6	3.2 ± 0.9	2.6 ± 1.0	0.05	NS	0.05	NS
Mitral inflow E-wave, m/s	0.67 ± 0.12	0.79 ± 0.22	0.67 ± 0.25	0.15	NS	NS	NS
Mitral inflow A-wave, m/s	0.53 ± 0.24	0.66 ± 0.19	0.52 ± 0.22	0.17	NS	NS	NS
Mitral inflow DT, ms	200 ± 69	208 ± 40	207 ± 69	0.90	NS	NS	NS
E' cm/s	7.9 ± 2.5	5.6 ± 1.7	4.6 ± 1.8	0.0002	0.01	<0.0001	NS
E/e' ratio	9.3 ± 2.6	14.6 ± 5.0	19.5 ± 16.6	0.03	0.03	0.02	NS
S' cm/s	7.1 ± 1.4	4.9 ± 1.2	3.7 ± 1.0	<0.0001	<0.0001	<0.0001	0.02
Right ventricle systolic pressure, mm Hg	24.6 ± 1.5	36.7 ± 11.0	38.0 ± 8.5	0.05	0.05	0.04	NS

Continued on the next page

Table 4 and Online Table 1. The best model to determine peak Vo_2 used parameters measured at peak exercise ($p = 0.03$ for nested models), but even models based on early stages of exercise improved the prediction compared with models using rest parameters ($p < 0.05$ for both). Determinants of effort capacity in controls were peak systemic vascular resistance ($p = 0.05$), peak AVo_2Diff ($p = 0.01$), peak heart rate ($p = 0.01$), and peak SV ($p = 0.01$); in HFpEF, peak LVEDV by E/e' ($p = 0.002$), peak heart rate ($p = 0.01$), peak AVo_2Diff ($p = 0.0003$), and peak SV ($p = 0.003$); and in HFrEF, peak AVo_2Diff ($p = 0.0004$), peak heart rate ($p = 0.02$), peak MR volume ($p = 0.05$), and peak SV ($p < 0.0001$).

VENTILATORY PARAMETERS. Ventilatory baseline parameters were worse in the HFpEF group (**Table 1**) and were significant univariate correlates of Vo_2 max in the entire cohort ($p < 0.0001$ for FVC and $p < 0.0001$ for forced expiratory volume first second [FEV_1]), and in each subgroup (controls $p = 0.0008$; HFpEF $p = 0.03$, HFrEF $p = 0.002$ for FVC; and

TABLE 1 Continued

	Controls (n = 14)	HFpEF (n = 16)	HFrEF (n = 15)	All	p Value: Control vs. HFpEF	p Value: Control vs. HFrEF	p Value: HFpEF vs. HFrEF
Cardiopulmonary stress test							
FVC, l	3.6 ± 1.3	2.8 ± 1.1	3.2 ± 0.9	0.20	NS	NS	NS
FVC, % predicted	87.4 ± 14.0	76.8 ± 21.0	81.6 ± 14	0.20	NS	NS	NS
FEV_1 l/s	3.3 ± 1.2	2.3 ± 0.8	2.8 ± 0.7	0.04	0.04	NS	NS
FEV, % predicted	95 ± 16	80.1 ± 19.0	89.5 ± 10	0.04	0.04	NS	NS
FEV_1/FVC ratio	89 ± 6	83.5 ± 12.0	88.5 ± 10	0.20	NS	NS	NS
FEV_1/FVC ratio, % predicted	111.3 ± 10.0	110.2 ± 15.0	115.7 ± 14	0.50	NS	NS	NS
Vo_2 @AT l/min	1.24 ± 0.4	0.87 ± 0.3	0.89 ± 0.3	0.0007	0.01	0.01	NS
Vo_2/kg @AT ml/min/kg	16.0 ± 5.4	10.5 ± 3.1	12.7 ± 7.5	0.03	0.02	NS	NS
Vo_2 @AT, % predicted max	58.4 ± 15.0	47.9 ± 12	45.4 ± 9	0.02	0.02	0.02	NS
Vo_2 @AT, % predicted AT	104.4 ± 27.0	84.6 ± 24	78.3 ± 17	0.01	0.01	0.01	NS
VE/Vco_2 ratio @AT	30.3 ± 4.8	35.8 ± 5.0	34.9 ± 4.2	0.008	0.03	0.02	NS
Work load, watts	180.6 ± 67.0	99.4 ± 46.0	115.7 ± 48	0.0006	0.0007	0.004	NS
Time of effort, min	11.1 ± 0.6	8.8 ± 0.6	9.8 ± 0.6	0.03	0.03	NS	NS
O_2 pulse max, ml/beat	12.6 ± 3.8	10.0 ± 4.1	11.7 ± 3.7	0.20	NS	NS	NS
Vo_2 max l/min	1.99 ± 0.7	1.23 ± 0.5	1.33 ± 0.6	0.002	0.003	0.006	NS
Vo_2 max, % predicted	92.6 ± 21.0	66.6 ± 21	67.6 ± 18.0	0.001	0.003	0.003	NS
Vo_2/kg max ml/min/kg	24.8 ± 8.7	14.7 ± 5.90	16.0 ± 6.3	0.0006	0.0008	0.003	NS
VO_2/kg, % predicted	94.6 ± 21.5	61.5 ± 21.7	63.6 ± 17.3	<0.0001	0.0002	<0.001	NS
Breathing reserve	61.9 ± 31.0	50.4 ± 22.0	64.3 ± 17.0	0.40	NS	NS	NS
MCR slope	0.93 ± 0.2	0.75 ± 0.17	0.77 ± 0.09	0.009	0.01	0.01	NS
RER ratio	1.12 ± 0.1	1.06 ± 0.1	1.05 ± 0.1	0.20	NS	NS	NS

Values are mean ± SD, n (%), or median [25th quartile, 75th quartile].

AT = anaerobic threshold; DT = deceleration time; FEV_1 = forced expiratory volume first second; FVC = forced vital capacity; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAVI = left atrial volume index; LV = left ventricle; MCR = metabolic chronotropic relationship; NS = not significant; O_2 pulse = oxygen consumption per cardiac cycle; RER = respiratory exchange ratio; VE = ventilation; Vco_2 = carbon dioxide output; Vo_2 = oxygen consumption.

p = 0.0007; HFpEF p = 0.01, HFrEF p = 0.01 for FEV_1). Remarkably, FVC remained a significant independent contributor to limitation of exercise capacity only in the HFpEF patients (controls p = 0.9, HFpEF p = 0.03, HFrEF p = 0.4).

EFFORT-INDUCED MR. Six patients with HFrEF and 2 patients with HFpEF developed unexpected (based on baseline EF and amount of MR) significant functional MR during stress, constituting the principal mechanism for effort intolerance. Importantly, functional MR developed at early stages of exercise (unloaded exercise), peaking during the anaerobic threshold, suggesting that the diagnosis of stress-induced MR does not require peak exercise (**Figure 1I**).

HFpEF BORDERLINE. Recent guidelines (19-22) have defined a new subgroup—HFpEF-borderline—with EF ranging between 41% and 49%, that fall between HFrEF and HFpEF. We have presented their data in Online Tables 2 and 3. The HFpEF borderline group had baseline and stress characteristics intermediate between those with HFpEF and HFrEF (Online Tables 2 and 3). Nevertheless, the only exception to the rule was effort-induced MR, which increased more in the intermediate patients than in the other groups (Online Table 3). Determinants of effort capacity in HFpEF borderline included LVEDV/E/e' (p = 0.0008), AVo_2Diff (p = 0.05), heart rate (p = 0.10) MR volume (p = 0.0006), and SV (p = 0.10), intermediate between those with HFpEF and HFrEF.

DISCUSSION

We evaluated the feasibility of a combined CPET and SE protocol to assess noninvasively multiple responses to dynamic exercise, in several predefined activity levels. Our major findings are that: 1) the combined protocol is feasible in most patients; 2) determinants of effort intolerance in both HFpEF and HFrEF include lower cardiac output, lower LV compliance, and higher peak systemic vascular resistance; and 3) in HFpEF and HFrEF patients, chronotropic incompetence and peripheral factors (low peak AVo_2Diff) play a major role in the pathogenesis of

TABLE 2 LV Dimensions, Function, and Hemodynamics Throughout Exercise Stages Among Normal Subjects, Patients With HFpEF, and Patients With HFrEF

Measurement	Baseline	Unloaded Effort	Anaerobic Threshold	Maximal Effort	p Value for Each Group	Within Group	Between Groups	Time-Group Interaction
End-diastolic volume, ml								
Normal	123.4 ± 20.0	138.8 ± 19.0†	158.3 ± 22.0†	133.3 ± 23.0†	<0.0001			
HFpEF	122.6 ± 18.0	128.6 ± 22.0	127.4 ± 18.0	118.1 ± 18.0	0.12	<0.0001	<0.0001	0.05
HFrEF	200.8 ± 59.0	222.4 ± 61.0*	218.4 ± 61.0	210.2 ± 50.0	0.10			
End-systolic volume, ml								
Normal	44 ± 13	37.6 ± 10.0	41.2 ± 16.0	36.7 ± 16.0	0.09			
HFpEF	41.1 ± 11.0	39.7 ± 12.0	35.0 ± 15.0	33.4 ± 17.0	0.09	0.01	<0.0001	0.08
HFrEF	127 ± 55	130.8 ± 52.0	120.3 ± 54.0	116.6 ± 52.0	0.06			
Ejection fraction, %								
Normal	64.7 ± 7.0	73.1 ± 6.0†	74.1 ± 9.0	73 ± 10	0.001			
HFpEF	66.5 ± 7.0	69.2 ± 6.0	72.8 ± 10.0	72.1 ± 11.0	0.06	<0.0001	<0.0001	0.04
HFrEF	38.8 ± 11.0	42.5 ± 14.0	47.2 ± 17.0	45.8 ± 16.0	0.07			
Tissue Doppler, S', cm/s								
Normal	7.1 ± 1.4	8.7 ± 2.3†	10.3 ± 1.9*	10.4 ± 2.3	0.01			
HFpEF	4.9 ± 1.2	5.9 ± 1.7*	7.7 ± 2.9	8.0 ± 2.8	0.01	<0.0001	0.002	0.20
HFrEF	3.7 ± 1.1	4.9 ± 1.8*	5.5 ± 2.2	6.1 ± 3.2	0.03			
Tissue Doppler, e', cm/s								
Normal	8.0 ± 2.5	9.9 ± 2.4†	14.7 ± 4.3†	17.8 ± 4.4†	<0.0001			
HFpEF	5.8 ± 1.7	6.9 ± 2.5*	8.1 ± 4.4	9.5 ± 5.0	0.03	<0.0001	<0.0001	0.0001
HFrEF	4.5 ± 1.7	5.6 ± 1.8	6.8 ± 3.0	7.2 ± 4.2	0.01			
E/e' ratio								
Normal	9.3 ± 3.9	9.6 ± 3.6	8.7 ± 3.0	7.6 ± 2.3	0.02			
HFpEF	14.6 ± 5.1	16.3 ± 5.8*	18.3 ± 10.3	17.8 ± 9.5	0.08	0.80	0.001	0.03
HFrEF	19.5 ± 16.6	22.0 ± 15.6	19.3 ± 11.6	21.4 ± 8.8	0.80			
Stroke volume, ml								
Normal	77.3 ± 10.0	92.1 ± 15.0†	105 ± 16†	98.6 ± 13.0	<0.0001			
HFpEF	78.8 ± 17.0	91 ± 20*	94.5 ± 24.0	86.7 ± 19.0*	0.007	<0.0001	0.006	0.0001
HFrEF	67.1 ± 20.0	67.5 ± 18.0	74.7 ± 27.0	70.7 ± 31.0	0.12			
O_2 pulse, ml/beat								
Normal	4.5 ± 1.1	6.5 ± 1.2†	10.3 ± 2.8†	12.7 ± 3.8†	<0.0001			
HFpEF	4.8 ± 1.2	6.7 ± 1.7*	8.9 ± 2.6*	11.3 ± 3.6†	<0.0001	<0.0001	0.40	0.30
HFrEF	4.7 ± 1.2	6.3 ± 1.7*	8.8 ± 2.9*	11.3 ± 3.9†	<0.0001			
Heart rate, beats/min								
Normal	80.2 ± 9.0	87.1 ± 11.0*	120.7 ± 20.0†	156 ± 20†	<0.0001			
HFpEF	76.6 ± 14.0	85.6 ± 15.0†	98.7 ± 22.0*	109.3 ± 31.0	<0.0001	<0.0001	0.001	0.0001
HFrEF	72.9 ± 9.0	85.9 ± 17.0†	97.5 ± 17.0	112.4 ± 20.0	<0.0001			
Cardiac output, l/min								
Normal	6.2 ± 1.1	8.0 ± 1.8†	12.6 ± 2.6†	14.5 ± 2.9*	<0.0001			
HFpEF	6.0 ± 1.5	7.7 ± 2.0†	9.4 ± 3.5*	9.6 ± 4.2	0.007	<0.0001	0.0001	<0.0001
HFrEF	4.9 ± 1.5	5.8 ± 1.3	7.0 ± 2.8	8.2 ± 4.4	0.10			
V_{O_2}, l/min								
Normal	0.36 ± 0.09	0.56 ± 0.13†	1.23 ± 0.37†	1.99 ± 0.67†	<0.0001			
HFpEF	0.37 ± 0.08	0.57 ± 0.19†	0.87 ± 0.27*	1.23 ± 0.51†	<0.0001	<0.0001	0.003	<0.0001
HFrEF	0.34 ± 0.09	0.56 ± 0.25†	0.87 ± 0.34*	1.29 ± 0.56†	<0.0001			
Mitral regurgitation, ml								
Normal	0.1 ± 0.3	1.2 ± 2.4	0.4 ± 1.0	1.2 ± 2.8	0.50			
HFpEF	4.2 ± 4.1	8.6 ± 3.4*	3.8 ± 6.6	3.7 ± 5.9	0.04	0.05	<0.0001	0.01
HFrEF	8.6 ± 13.5	24.0 ± 27.0*	21.3 ± 22.0	23.9 ± 22.8	0.05			
Systemic vascular resistance, dyne*s/cm								
Normal	1,168 ± 479	1,012 ± 264†	649 ± 225†	627 ± 164	<0.0001			
HFpEF	1,285 ± 537	1,156 ± 262†	993 ± 320	1,095 ± 449	0.004	<0.0001	0.004	0.02
HFrEF	1,544 ± 511	1,210 ± 460	1,349 ± 749	1,353 ± 802	0.30			
EDV/E:e' ratio								
Normal	15.5 ± 7.0	16.3 ± 6.0	19.9 ± 7.0*	19.1 ± 8.0	0.02			
HFpEF	9.5 ± 4.0	9.5 ± 5.0	9.3 ± 5.0	8.3 ± 4.0	0.20	0.30	0.004	0.01
HFrEF	16.1 ± 11.0	14.7 ± 10.0	14.1 ± 8.0	11.6 ± 5.0	0.07			

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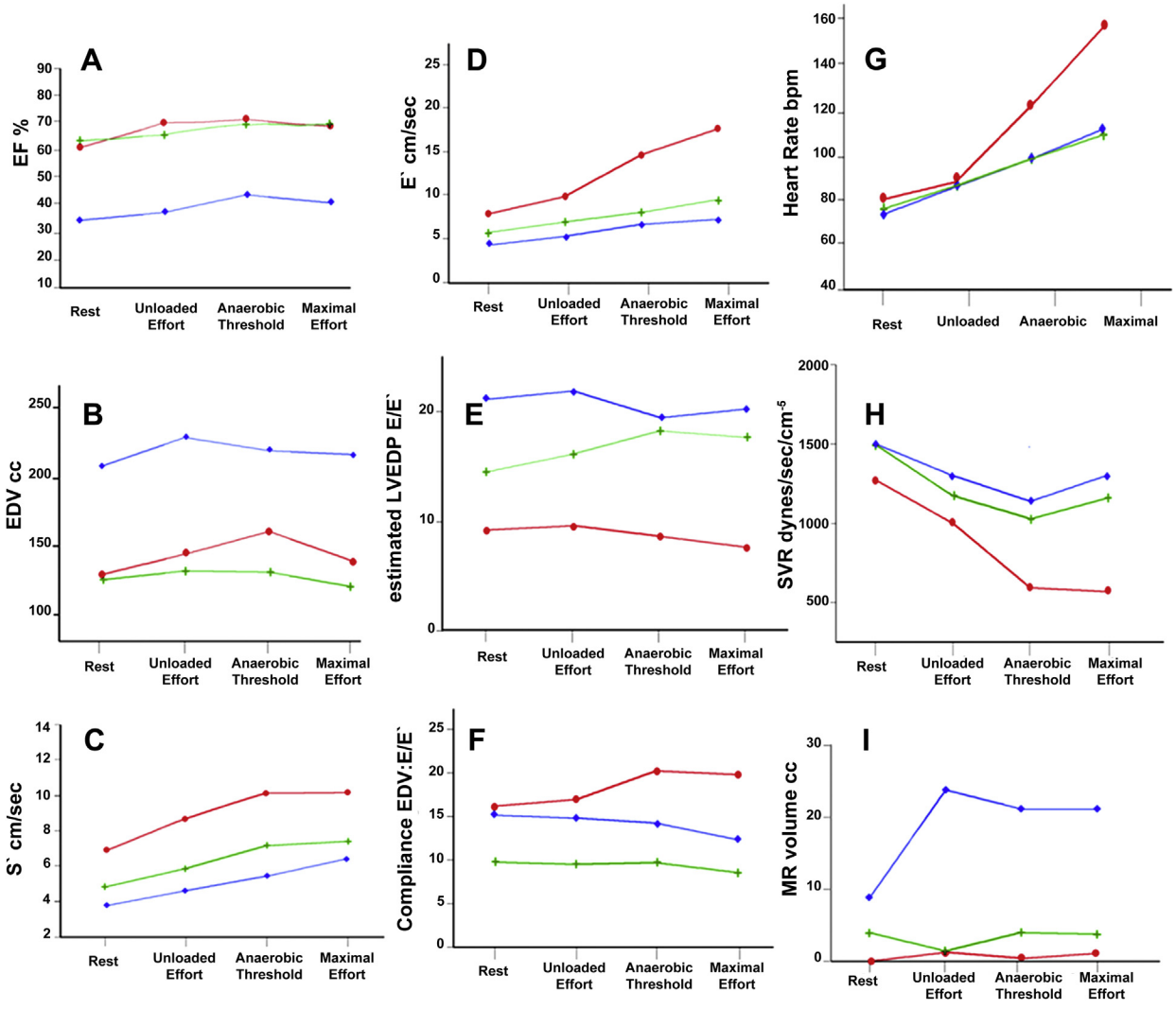
TABLE 2 Continued

Measurement	Baseline	Unloaded Effort	Anaerobic Threshold	Maximal Effort	p Value for Each Group	Within Group	Between Groups	Time-Group Interaction
Avo_2diff, l/l								
Normal	0.06 ± 0.01	0.07 ± 0.11†	0.10 ± 0.02†	0.13 ± 0.03†	<0.0001			
HFpEF	0.06 ± 0.02	0.07 ± 0.02	0.10 ± 0.03†	0.13 ± 0.05†	<0.0001	<0.0001	0.06	0.80
HFrEF	0.08 ± 0.03	0.09 ± 0.02*	0.12 ± 0.02*	0.14 ± 0.01*	0.02			

Values are mean ± SD, or n (%). *p < 0.01; †p < 0.001.
AVo_2Diff = arterial-venous oxygen content difference; EDV = end-diastolic volume; other abbreviations as in Table 1.

FIGURE 1 Echo Parameters at Baseline, Unloaded, Anaerobic Threshold, and Maximal Exercise Tests in the Study Groups



(A to I) Baseline, unloaded, anaerobic threshold, and maximal cardiopulmonary exercise tests and stress echocardiography characteristics of heart failure with preserved ejection fraction **(green crosses)**, heart failure with reduced ejection fraction **(blue diamonds)**, and controls **(red circles)**. AT= anaerobic threshold; Vco_2 = carbon dioxide output; Vo_2 = oxygen consumption.

TABLE 3 Univariate Analyses to Explore the Contribution of the Different Rest, Unloaded, AT, and Peak Parameters on Maximal Effort Capacity (Vo_2max)

	R value	Regression Coefficient ± SE	p Value
Age, yrs	-0.26	-0.11 ± 0.006	0.07
Male		0.06 ± 0.11	0.50
Height, m	0.44	0.006 ± 0.006	0.001
Weight, kg	0.22	0.016 ± 0.02	0.50
Body mass index, kg/m^2	0.07	0.011 ± 0.02	0.60
Creatinine, mg/dl	0.05	0.08 ± 0.30	0.80
Hemoglobin, g/dl	0.56	0.11 ± 0.07	0.006
Charlson score	-0.22	-0.05 ± 0.05	0.20
Ejection fraction, %	0.22	0.01 ± 0.06	0.10
Diastolic dimension, mm	-0.03	-0.002 ± 0.01	0.90
Systolic dimension, mm	-0.08	-0.005 ± 0.008	0.60
End-diastolic volume, ml	-0.17	-0.0006 ± 0.002	0.70
End-systolic volume, ml	-0.14	-0.002 ± 0.002	0.30
LV mass index, g/m^2	-0.17	-0.003 ± 0.002	0.20
Relative wall thickness	-0.26	-0.42 ± 0.80	0.60
LAVI, ml/m^2	-0.49	-0.02 ± 0.005	0.0006
Stroke volume, ml/beat	0.20	0.008 ± 0.005	0.20
Cardiac output, l/min	0.30	0.14 ± 0.06	0.04
Mitral inflow E-wave m/s	-0.41	-0.01 ± 0.004	0.004
Mitral inflow A-wave m/s	-0.26	-0.008 ± 0.004	0.09
Mitral inflow DT, ms	0.10	0.001 ± 0.002	0.50
E' cm/s	0.68	0.18 ± 0.03	0.0001
E/e' ratio	-0.54	-0.03 ± 0.008	0.0001
End-diastolic volume for E/e'	0.60	0.05 ± 0.0009	<0.0001
S' cm/s	0.71	0.26 ± 0.04	<0.0001
MR volume	-0.008	-0.006 ± 0.01	0.60
Systemic vascular resistance, dyne/s/cm	-0.10	-0.0001 ± 0.0002	0.50
Right ventricle systolic pressure, mm Hg	-0.44	-0.03 ± 0.01	0.04
End-diastolic volume change % to unloaded	0.33	0.02 ± 0.009	0.02
End-diastolic volume change % to AT	0.57	0.02 ± 0.004	<0.0001
End-diastolic volume change % to max	0.22	0.009 ± 0.005	0.12
End-diastolic volume for E/e' change to unloaded	0.68	0.40 ± 0.07	<0.0001
End-diastolic volume for E/e' change to AT	0.76	0.27 ± 0.03	<0.0001
End-diastolic volume for E/e' change to max	0.38	0.15 ± 0.06	0.01
Ejection fraction, unloaded	0.30	0.012 ± 0.0006	0.07
Ejection Fraction, AT	0.28	0.012 ± 0.006	0.05
Ejection fraction, max	0.31	0.013 ± 0.006	0.05
Tissue Doppler S', cm/s unloaded	0.74	0.21 ± 0.03	<0.0001
Tissue Doppler S', cm/s AT	0.67	0.16 ± 0.03	<0.0001
Tissue Doppler S', cm/s max	0.68	0.11 ± 0.02	<0.0001
Tissue Doppler e', cm/s unloaded	0.78	0.18 ± 0.02	0.0003
Tissue Doppler e', cm/s AT	0.79	0.08 ± 0.01	0.0003
Tissue Doppler e', cm/s max	0.68	0.07 ± 0.01	0.0002
E/e' ratio unloaded	-0.63	-0.05 ± 0.01	0.0001
E/e' ratio AT	-0.66	-0.04 ± 0.008	0.0001
E/e' ratio max	-0.69	-0.05 ± 0.009	0.0001
Stroke volume, ml unloaded	0.53	0.017 ± 0.004	0.0005
Stroke volume, ml AT	0.73	0.02 ± 0.003	<0.0001

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exercise intolerance. The study provides several novel insights. First, HFpEF patients, although having less exercise-induced MR than HFrEF, nonetheless have more than controls and it may contribute to their exertion symptoms. Second, HFpEF patients have significant ventilatory abnormalities, even compared with HFrEF, where abnormalities have been reported previously (20). In addition to these novel insights, the study provides strong confirmation of an important, evolving theme in HF physiology, namely, the contribution of peripheral, presumed skeletal muscle, abnormalities, to exercise intolerance.

DETERMINANT OF EFFORT INTOLERANCE. Chronotropic incompetence. Peak heart rate was decreased, and heart rate reserve increased in both HF groups. This phenomenon has been observed in patients with HFpEF (5,14), or HFrEF (21–23). Even though β-blocker and calcium-channel blocker therapy were left unchanged, we were able to show that chronotropic incompetence was common in the HFpEF and HFrEF groups (13% control, 60% HFpEF, 64% HFrEF; p = 0.005), even when using the criteria used in the presence of β-blocker therapy (16), and was a strong predictor of effort intolerance. Although peak SV correlated with exercise capacity in non-adjusted analyses, it was deleted from the multivariate model by peak heart rate and AVo_2Diff, suggesting that in HF patients exercise intolerance is predominantly due to chronotropic incompetence and peripheral factors.

AVo_2Diff and effort intolerance in HF. We found that, in addition to cardiac output, peak AVo_2Diff was an independent predictor of peak Vo_2 in all groups. This finding is not surprising, given that capacity for both oxygen delivery and use plays an important role in limiting exercise performance (17,24–28). Our findings confirms previous findings that have shown that abnormalities in skeletal muscle characteristics (increased glycolytic metabolism, metabolic inefficiency, lower perfusion) play an important role in reduced effort capacity in patients with HFpEF (24,26,27) or HFrEF (29–31). Importantly, our noninvasive protocol may imply decreased AVo_2Diff as a contributing cause of effort intolerance even in patients with severe rest systolic dysfunction (Online Figure 2), indicating a possible advantage of endurance exercise training and allowing possible delays in device therapy.

LV diastolic pressure and compliance. E/e', the echocardiography correlate of LV diastolic pressure, did not change significantly during exercise, although it differed between the patients with and without HF. Interestingly, in multivariate analysis, E/e' and SV were not independent contributors to decreased exercise capacity, as opposed to LVEDV/E/e' ratio, suggesting that increased LV pressure, or low SV per se, are not the primary causes of effort intolerance. The LVEDV/E/e' ratio, which removed both peak E/e' and

peak SV from the final multivariate model, may represent the inability of the LV to increase its size, even with a high filling pressure. Nevertheless, these findings should be considered hypothesis generating and should be tested with prospective invasive methods.

Ventilatory abnormalities. It has long been known that HFrEF have significant ventilatory abnormalities that can contribute to exercise intolerance (20,32). We found that baseline ventilatory parameters were worse in the HFpEF compared with other groups and contributed independently to limitation of exercise capacity, suggesting that in HFpEF ventilatory abnormalities have a prominent role in effort intolerance, even compared with HFrEF.

Stress-induced functional MR. Exercise is an important cause of variability in functional MR, and the degree of MR at the anaerobic threshold or peak exercise is a strong determinant of effort capacity, irrespective of the baseline EF and MR. The normal response to exercise involves vasodilation (reducing tethering forces) and improved contractility, increasing closing forces. However, a hypertensive response to exercise or loss of contractile reserve may all lead to worsening MR with exercise. The wide range of exercise-induced changes in MR observed were unrelated to the degree of MR or EF at rest, but were exposed even by minor degrees of exercise, suggesting that assessment of exercise-induced functional MR does not require maximal exercise.

COMBINED CARDIOPULMONARY AND ECHOCARDIOGRAPHY EXERCISE PROTOCOL. Most previous CPET studies performed to examine the determinants of exercise used invasive assessment of cardiac output and radionuclide ventriculography. They were limited by their invasive nature, which limits the widespread clinical applicability, and may cause selection bias (1,5,29,33). Recent studies have used combined echocardiography and cardiopulmonary exercise protocols (17,24,25,34) similar to ours. Nevertheless, our protocol differs in several important aspects from those reported previously. First, we did not use a fixed initial power output and a predetermined increase in work. Instead, we calculated the expected work and calculated the work rate increment necessary to reach the patient's estimated peak work in 8 to 12 min. This allowed enough time to acquire echocardiography images, including comprehensive Doppler hemodynamic data, allowing calculation of compliance (LVEDV by E/e' ratio) and functional MR 4 times during the protocol, even in the sickest patients. Second, we obtained echocardiography images at individual stages of effort (rest, anaerobic threshold, maximal) instead of preselected power outputs, which may represent different stages of effort in different patients. Third, we did not withdraw β-blocker and calcium blocker therapy during the examination because

TABLE 3 Continued

	R value	Regression Coefficient ± SE	p Value
Stroke volume, ml max	0.68	0.02 ± 0.004	<0.0001
Heart rate, beats/min unloaded	0.02	0.003 ± 0.009	0.60
Heart rate, beats/min AT	0.52	0.016 ± 0.004	0.0004
Heart rate, beats/min max	0.72	0.014 ± 0.002	<0.0001
Chrontropic incompetence (yes/no)		-0.38	<0.0001
HRR		-0.01 ± 0.002	<0.0001
Cardiac output, l/min unloaded	0.46	0.16 ± 0.05	0.002
Cardiac output, l/min AT	0.77	0.14 ± 0.02	<0.0001
Cardiac output, l/min max	0.87	0.13 ± 0.01	<0.0001
MR volume, unloaded	-0.08	-0.006 ± 0.005	0.20
MR volume, AT	-0.09	-0.007 ± 0.006	0.30
MR volume, max	-0.20	-0.01 ± 0.005	0.02
Systemic vascular resistance, dyne/s/cm, unloaded	-0.64	-0.001 ± 0.0003	0.001
Systemic vascular resistance, dyne/s/cm, AT	-0.63	-0.0008 ± 0.0001	<0.0001
Systemic vascular resistance, dyne/s/cm, max	-0.69	-0.0008 ± 0.0001	<0.0001
End-diastolic volume for E/e' unloaded	0.70	0.06 ± 0.0009	<0.0001
End-diastolic volume for E/e' AT	0.82	0.07 ± 0.007	<0.0001
End-diastolic volume for E/e' max	0.75	0.07 ± 0.009	<0.0001
AVo_2Diff unloaded	-0.09	-1.2 ± 5.5	0.80
AVo_2Diff AT	0.04	2.8 ± 4.0	0.50
AVo_2Diff max	0.31	5.6 ± 3.1	0.05

LAVI = left atrial volume index; MR = mitral regurgitation; other abbreviations as in Tables 1 and 2.

TABLE 4 Multivariate Analyses to Explore the Contribution of the Different Parameters on Maximal Effort Capacity

Parameter	Vo_2 by AT Regression Coefficient; p Value	Vo_2 by Max Regression Coefficient; p Value
Age, yrs	p = 0.90	p = 0.30
LAVI, ml/m^2	–	–
Cardiac output rest	–	–
EDV for E/e' rest	p = 0.40	p = 0.20
S' rest	p = 0.20	p = 0.70
EF rest	–	–
E/e' ratio rest	–	–
HR, stress	p = 0.20	p = 0.007
EDV for E/e' stress	0.05; p < 0.0001	0.04; p = 0.0001
Systemic vascular resistance stress	p = 0.40	-0.001; p = 0.05
S' stress	p = 0.20	p = 0.30
EF, stress	p = 0.50	p = 0.15
MR volume, stress	–	p = 0.80
Avo_2Diff stress	–	7.02; p < 0.0001
p value	<0.0001	<0.0001
R^2	0.83	0.94

we sought to determine the individual factors responsible for effort intolerance in course of "real-life" medical regiment, which allowed us to give specific recommendations for each individual subject.

CLINICAL IMPLICATIONS. Our data provide confirmation that chronotropic incompetence and peripheral muscle factors are major contributors to exercise intolerance in HF patients, irrespective of EF; thus, therapies directed only at improving cardiac function may never improve exercise capacity in HF. In regard to treatment directed at chrontropic incompetence in HF, 2 major interventions have been investigated, endurance training, demonstrated to increase peak heart rate by 5% to 7% (14), and rate-adaptive pacing. The potential benefit of rate-adaptive pacing for exercise performance in HFrEF patients was assessed recently (35), and was shown to be beneficial in HFrEF patients with severe chrontropic incompetence (achieving <70% of age-predicted maximal heart rate). Although rate-adaptive pacing has potential benefit in carefully selected patients with HFrEF, less is known regarding pacing in patients with HFpEF. As to potential treatments for the skeletal myopathy of HF, numerous interventions have been investigated. These include angiotensin-converting enzyme inhibitors, adrenergic blockade, therapies directed at restoring excitation-contraction coupling in skeletal muscles, and molecular therapies for skeletal myopathy (36).

STUDY LIMITATIONS. We cannot exclude that continued effects of β-blocker may have influenced the blunted HR response. However, the results were unchanged when adjustments were performed for long-term β-blocker use. Our SV and cardiac output measurements may have been underestimated or overestimated due to the technical challenge of acquiring echocardiography images during exercise. However, this technique has been validated and reported excellent day-to-day reproducibility and intraobserver and interobserver variability (10,17,24,25). The AVo_2Diff was not measured, but was calculated using the Fick equation as Vo_2/cardiac output. The calculated peak AVo_2 in our subjects is somewhat lower than that previously reported by others (10,17,24,25). However, the pattern of our results is similar to those reported previously, in which the AVo_2Diff was measured invasively (1,29,37). Although individual etiologies for effort intolerance implied by the combined test are intriguing, they should be considered hypothesis generating, and need to be tested in adequately powered, prospective, randomized, controlled, and blinded fashion before they can be suggested for use in patient management. Until then, we caution against the use of the echocardiography–Doppler exercise findings in individual patient management. Our imaging protocol was performed in the semisupine position. Because the Starling mechanism depends on gravity and venous pooling, generalizing our observations to other types of exercise (supine or upright) warrants future studies in each specific context. Our groups were not well-matched; there was a great age and sex difference in the control group, and heart rates in the HF patients are much lower. Because there are known age-associated changes in cardiac, vascular, and skeletal muscle function, our data should be interpreted with caution, considered preliminary, and confirmed in further studies. The magnitude of the peripheral contribution to reduced exercise capacity in the HFpEF patients (via reduced AVo_2Diff) may be even greater than observed in our study, which may have systematically underestimated it by assigning patients with clinically important dyspnea of unknown origin who had significantly decreased AVo_2Diff compared to the control group. This is particularly relevant; the 2013 HF (19) management guidelines do not require abnormal diastolic function, or any cardiac imaging abnormality for diagnosis of HFpEF, which is largely a diagnosis of exclusion. Finally, by study design, participants were ambulatory outpatients and were physically able to participate in exhaustive exercise testing. As a result, the study population was predominantly in New York Heart Association functional class II or III.

CONCLUSIONS

Combined CPET and stress echocardiography tests are feasible in most subjects and allow the noninvasive evaluation of effort intolerance. Chronotropic incompetence and decreased peripheral oxygen extraction played a major role in effort intolerance in both HFpEF and HFrEF. This finding suggests that interventions that optimize peak heart rate, skeletal muscle perfusion, or oxygen extraction by the active muscles may improve peak exercise performance in individual patients. Furthermore, this technique may have potential for clinical management and selection of patients for trials.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The heterogeneity of the HFpEF and HFrEF population poses a major challenge to development of therapies to treat HF. A potential solution is to identify subjects in whom the majority of reduction in peak Vo_2 is attributable to an abnormality in one of the components of peak Vo_2. In this study, combined CPET with echocardiography and noninvasive hemodynamic measurements permitted us to evaluate each component of Vo_2 to subclassify patients on the basis of the dominant mechanism limiting exercise capacity. This approach may improve patient selection for targeted therapeutics; for example, HF patients could be classified into those with primarily impaired peripheral O_2 extraction, chronotropic incompetence, or impaired SV response and be treated accordingly. Furthermore, our study highlights the significant role of impaired peripheral oxygen extraction in contributing to exercise intolerance in HFpEF and HFrEF patients.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the effect of targeting different aspects of the limits to the peak Vo_2. Although individual etiologies for effort intolerance implied by the combined echocardiography and cardiopulmonary stress tests are intriguing, they should be considered hypothesis generating, and need to be tested in adequately powered, prospective, randomized, controlled, and blinded fashion before they can be suggested for use in individual patient management.

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KEY WORDS congestive heart failure, echocardiography, exercise testing

APPENDIX For supplemental tables and figures, please see the online version of this article.