JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 6, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.10.096

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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Manuscript received September 8, 2015; revised manuscript received October 13, 2015, accepted October 29, 2015.

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.

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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

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