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Cardiac Imaging

Impaired Systolic Function by Strain Imaging in Heart Failure With Preserved Ejection Fraction

Elisabeth Kraigher-Krainer, MD,* Amil M. Shah, MD, MPH,* Deepak K. Gupta, MD,* Angela Santos, MD,* Brian Claggett, PHD,* Burkert Pieske, MD,† Michael R. Zile, MD,‡ Adriaan A. Voors, MD,§ Marty P. Lefkowitz, MD,|| Milton Packer, MD,¶ John J. V. McMurray, MD,# Scott D. Solomon, MD,* for the PARAMOUNT Investigators

Boston, Massachusetts; Graz, Austria; Charleston, South Carolina; Groningen, the Netherlands; East Hanover, New Jersey; Dallas, Texas; and Glasgow, United Kingdom

Objectives This study sought to determine the frequency and magnitude of impaired systolic deformation in heart failure with preserved ejection fraction (HFpEF).

Background Although diastolic dysfunction is widely considered a key pathophysiologic mediator of HFpEF, the prevalence of concomitant systolic dysfunction has not been clearly defined.

Methods We assessed myocardial systolic and diastolic function in 219 HFpEF patients from a contemporary HFpEF clinical trial. Myocardial deformation was assessed using a vendor-independent 2-dimensional speckle-tracking software. The frequency and severity of impaired deformation was assessed in HFpEF, and compared to 50 normal controls free of cardiovascular disease and to 44 age- and sex-matched hypertensive patients with diastolic dysfunction (hypertensive heart disease) but no HF. Among HFpEF patients, clinical, echocardiographic, and biomarker correlates of left ventricular strain were determined.

Results The HFpEF patients had preserved left ventricular ejection fraction and evidence of diastolic dysfunction. Compared to both normal controls and hypertensive heart disease patients, the HFpEF patients demonstrated significantly lower longitudinal strain (LS) (-20.0 ± 2.1 and -17.07 ± 2.04 vs. -14.6 ± 3.3, respectively, $p < 0.0001$ for both) and circumferential strain (CS) (-27.1 ± 3.1 and -30.1 ± 3.5 vs. -22.9 ± 5.9, respectively; $p < 0.0001$ for both). In HFpEF, both LS and CS were related to LVEF (LS, $R = -0.46$; $p < 0.0001$; CS, $R = -0.51$; $p < 0.0001$) but not to standard echocardiographic measures of diastolic function (E' or E/E'). Lower LS was modestly associated with higher NT-proBNP, even after adjustment for 10 baseline covariates including LVEF, measures of diastolic function, and LV filling pressure (multivariable adjusted $p = 0.001$).

Conclusions Strain imaging detects impaired systolic function despite preserved global LVEF in HFpEF that may contribute to the pathophysiology of the HFpEF syndrome. (LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; NCT00887588) (J Am Coll Cardiol 2014;63:447–56) © 2014 by the American College of Cardiology Foundation

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and growing public health problem associated with significant morbidity and an increased risk of in-hospital, short-term, and long-term mortality (1,2). Impairment in LV diastolic function has been proposed as a key pathophysiologic mediator (3–5). However, the role of concomitant systolic dysfunction despite preserved left ventricular ejection fraction (LVEF) has not been well characterized, but may help inform future treatment

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From the *Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; †Medical University Graz, Graz, Austria; ‡RHJ Department of Veterans Affairs, Medical Center and Medical University of South Carolina, Charleston, South Carolina; §University of Groningen, Groningen, the Netherlands; ||Novartis Pharmaceuticals, East Hanover, New Jersey; ¶University of Texas Southwestern, Dallas, Texas; and the #University of Glasgow, Glasgow, United Kingdom. Drs. Solomon, Shah, Zile, Pieske, Voors, Packer, and McMurray have received research support from and/or have consulted for Novartis. Dr. Pieske is on the Steering Committee of the PARAMOUNT study and receives moderate compensation. Dr. Lefkowitz is an employee of Novartis. All other authors have reported they have no relationships relevant to the contents of this paper to disclose. Drs. Kraigher-Krainer and Shah contributed equally to this manuscript.

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Abbreviations and Acronyms

CS = circumferential strain
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HHD = hypertensive heart disease
LA = left atrial
LAVi = left atrial volume index
LV = left ventricular
LVEF = left ventricular ejection fraction
LS = longitudinal strain
NT-proBNP = N-terminal pro-brain natriuretic peptide
RWT = relative wall thickness

strategies by defining subphenotypes in this heterogeneous population. Indeed, prior studies suggest that LV longitudinal function assessed by tissue Doppler imaging may be impaired in HFpEF (6–11). However, tissue Doppler-based assessment of LV longitudinal function is angle dependent and typically assesses only mitral annular motion.

More recently, B-mode speckle tracking has allowed for quantitative assessment of LV deformation, and abnormalities of strain and strain rate have been described in HFpEF in several small single-center studies (12–15). We employed myocardial deformation imaging to determine the frequency, severity, and correlates of impaired systolic function among patients with HFpEF enrolled in a contemporary multicenter clinical trial. Specifically, we hypothesized that despite preserved LVEF, abnormal strain would be prevalent in HFpEF, differentiate HFpEF from asymptomatic hypertensive heart disease (HHD), and would relate to levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a soluble biomarker of myocardial wall stress with prognostic relevance in HFpEF, independent of measures of diastolic function.

Methods

Patient population. The PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial) study enrolled patients with signs and symptoms of heart failure (HF), New York Heart Association class II to IV symptoms, LVEF ≥45%, and NT-proBNP level >400 pg/ml. Patients were randomly allocated to receive either the angiotensin-receptor neprilysin inhibitor (ARNI) LCZ696 or valsartan over a period of 12 weeks. The study protocol was approved by all individual site institutional review boards and ethics committees, and all recruited patients gave written informed consent. Details of the inclusion and exclusion criteria, study design and primary findings have been previously reported (16). Screening NT-proBNP was established by a tabletop device at point of care, local laboratory, or central laboratory. No NT-proBNP data were available for the HHD group or control population.

Control group. We screened the Brigham and Women's Hospital's echocardiography database to retrospectively identify normal control subjects. Echocardiographic examinations were clinically indicated for 1 of the following reasons: murmur, evaluation of LV function, syncope, or atypical chest pain. Normal echocardiograms were defined as normal LV size and geometry, normal LVEF (>55%), normal left atrial volume index (LAVi) (<29 ml/m^2) (17), no stenotic valvular lesion, and no abnormal valvular regurgitation. Electronic medical records were reviewed for prevalent cardiovascular disease (stroke, coronary artery disease, myocardial infarction, revascularization, heart failure, arrhythmia, peripheral artery disease), cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, renal dysfunction), systemic disease (such as cancer, infections, autoimmune disorders), or any pharmacotherapy. Subjects were excluded if any of these were identified. In all, 2,100 echocardiographic examinations and medical records performed between 2010 and 2012 were screened to identify 50 controls of similar age and sex distribution as our HFpEF cohort.

Hypertensive group with diastolic dysfunction but no HF. We identified 44 patients with hypertension and diastolic dysfunction matched to the HFpEF population for age and sex. They were selected from patients enrolled in the EXCEED (Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic dysfunction) trial. Details of the inclusion and exclusion criteria, study design, and primary findings have been previously published (18,19). Briefly, the EXCEED trial was a multicenter, open-label study of patients ≥45 years of age with a history of uncontrolled systolic hypertension, preserved LVEF (≥50%), and echocardiographic evidence of diastolic dysfunction. Patients with HF symptoms, secondary hypertension, diabetes, atrial fibrillation, a vascular event within the prior 6 months, serum creatinine >2.0 mg/dl, or nephrotic syndrome were excluded. All participants underwent echocardiography at enrollment, which was analyzed centrally by the same core laboratory as the PARAMOUNT study (Brigham and Women's Hospital, Boston, Massachusetts).

Echocardiographic analyses. All sonographers at participating sites underwent central training in the details of the echocardiographic views and techniques at study investigator meetings. Echocardiograms were performed at study enrollment and were sent on digital storage media to the echocardiography core laboratory at Brigham and Women's Hospital. Conventional echocardiographic analysis including 2-dimensional, Doppler, and tissue Doppler were performed by technicians blinded to clinical information and treatment assignment using an offline analysis work station, as previously described in detail (20). Ventricular volumes were calculated by the modified Simpson's method using the apical 4- and 2-chamber views, and LVEF was derived from volumes in the standard manner (17). The LV mass was calculated from LV linear dimensions and indexed to body surface area as recommended by American Society of Echocardiography guidelines. Left ventricular hypertrophy was defined as LV mass indexed to body surface area (LVMi) >115 g/m^2 in men or >95 g/m^2 in women. The relative wall thickness (RWT) was calculated from LV end-diastolic dimension and posterior wall thickness. The left atrial (LA) volume was measured by the biplane

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