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Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Optimal patient characterization in heart failure with preserved ejection fraction (HFpEF) is essential to tailor successful treatment strategies. Cardiac magnetic resonance (CMR)-derived T_1 mapping can noninvasively quantify diffuse myocardial fibrosis as extracellular volume fraction (ECV).

OBJECTIVES This study aimed to elucidate the diagnostic performance of T_1 mapping in HFpEF by examining the relationship between ECV and invasively measured parameters of diastolic function. It also investigated the potential of ECV to differentiate among pathomechanisms in HFpEF.

METHODS We performed T_1 mapping in 24 patients with HFpEF and 12 patients without heart failure symptoms. Pressure-volume loops were obtained with a conductance catheter during basal conditions and handgrip exercise. Transient pre-load reduction was used to extrapolate the diastolic stiffness constant.

RESULTS Patients with HFpEF showed higher ECV ($p < 0.01$), elevated load-independent passive left ventricular (LV) stiffness constant (beta) ($p < 0.001$), and a longer time constant of active LV relaxation ($p = 0.02$). ECV correlated highly with beta ($r = 0.75$; $p < 0.001$). Within the HFpEF cohort, patients with ECV greater than the median showed a higher beta ($p = 0.05$), whereas ECV below the median identified patients with prolonged active LV relaxation ($p = 0.01$) and a marked hypertensive reaction to exercise due to pathologic arterial elastance ($p = 0.04$). On multiple linear regression analyses, ECV independently predicted intrinsic LV stiffness ($\beta = 0.75$; $p < 0.01$).

CONCLUSIONS Diffuse myocardial fibrosis, assessed by CMR-derived T_1 mapping, independently predicts invasively measured LV stiffness in HFpEF. Additionally, ECV helps to noninvasively distinguish the role of passive stiffness and hypertensive exercise response with impaired active relaxation. (Left Ventricular Stiffness vs. Fibrosis Quantification by T_1 Mapping in Heart Failure With Preserved Ejection Fraction [STIFFMAP]; NCT02459626) (J Am Coll Cardiol 2016;67:1815–25) © 2016 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) is an increasingly common condition accounting for almost one-half of heart failure (HF) cases, thus presenting a major challenge in modern cardiology (1). The prognosis of patients with HF symptoms and sustained systolic function is comparable to patients with reduced systolic function (2). Despite extensive research, all efforts to develop successful treatment strategies have led to unsatisfactory results (3–6). The lack of consistent therapeutic success might partly be explained by the heterogeneous cohort of patients investigated in previous studies, who exhibit exercise intolerance elicited by different pathophysiological mechanisms (7–11). Thus, there is a need to optimize patient characterization to enable scientists and clinicians to successfully tailor individual treatments.

Diastolic dysfunction can frequently be diagnosed in HFpEF patients and is associated with an impairment of active left ventricular (LV) relaxation and/or

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ABBREVIATIONS AND ACRONYMS

beta = left ventricular stiffness constant

Ea = arterial elastance

ECV = extracellular volume fraction

EDPVR = end-diastolic pressure volume relation

Ees = end-systolic elastance

ESPVR = end-systolic pressure-volume relations

PV = pressure volume

tau = time-constant of active left ventricular relaxation

LV compliance, which in turn results in a disproportional rise in LV filling pressures during exercise (7,12).

Diffuse myocardial fibrosis and an increase in extracellular matrix have been suggested as potential mechanisms for increased LV stiffness and diastolic dysfunction (13–15).

Cardiac magnetic resonance (CMR) imaging is a noninvasive tool that allows reliable characterization of myocardial tissue. With the recent advent of T_1 mapping techniques, it has become possible to quantify diffuse changes to the extracellular space. Post-contrast T_1 times and extracellular volume fraction (ECV) correlate with histological collagen volume fraction in vivo and in vitro (16,17). The diagnostic value of T_1 mapping techniques in patients with HFpEF needs to be further determined.

Invasive tracings of pressure-volume (PV) relations represent the gold standard for assessing left ventricular (LV) load-independent mechanical diastolic properties. Moreover, this technique provides the opportunity to instantly assess different aspects of diastolic function and the end-diastolic pressure-volume relation (EDPVR) under altering loading conditions (18,19).

SEE PAGE 1826

This study examined the relationship between ECV and invasively measured parameters of diastolic function, and also investigated the potential of ECV to differentiate between different pathomechanisms in HFpEF.

METHODS

This was a prospective study conducted at the Heart Center, Leipzig University, Germany. Patients with clinical and echocardiographic evidence for HFpEF were included, and patients without HF symptoms but indication for invasive coronary angiography served as control subjects. HFpEF patients were identified according to a consensus paper of the European Society of Cardiology (20), using specific inclusion criteria: left ventricular ejection fraction (LVEF) ≥50%; New York Heart Association functional class ≥II; and E/E′ (explanation in next section) 15 or E/E′ 8 to 15 combined with elevated B-type natriuretic peptide. Patients without HF symptoms served as control subjects; specific inclusion criteria were LVEF >50%, E/E′ <8, as well as normal values of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Exclusion criteria included any relevant coronary artery diseases (CADs), any contraindication to CMR imaging (e.g., pacemaker or cardioverter-defibrillator implants), an estimated glomerular filtration rate <30 ml/min/1.73 m^2, acute coronary syndrome, more than moderate valvular diseases, or persistent atrial fibrillation. NT-proBNP levels were analyzed centrally with a standard assay (Cobas, Elecsys NT-proBNP II, Roche, Basel, Switzerland). Assay-specific elevations >220 pg/ml were considered relevant.

To ensure comparable levels of intravascular volumes, CMR imaging and cardiac catheterization were preceded by an intravenous infusion of 500 ml saline solution. To reduce significant confounding, oral medication was withheld on the day of diagnostic workup.

The study was approved by the local ethics committee, and all patients gave written informed consent.

IMAGING AND TESTING PROTOCOLS. Echocardiographic studies were performed on a Vivid 9 system (General Electric Healthcare, Chalfont St. Giles, Great Britain). Mitral valve inflow pattern (E and A velocity), septal and lateral mitral valve annular velocities (E′), as well as the duration of the A wave and the duration of the pulmonary venous flow reversal (Ar), were recorded in an apical 4-chamber view. The ratios of E/A, E/E′ septal, E/E′ lateral, an averaged E/E′, and the difference of Ar-A duration were calculated as markers of diastolic function according to American Society of Echocardiography guidelines (21). Data were analyzed from stored images by an experienced operator (M.vR.) who was unaware of other test results. Measurements were made in 3 cardiac cycles; the average was used for statistical analysis.

Cardiopulmonary exercise testing was performed on a bicycle ergometer. Work rate was increased with a ramp protocol. Breath-by-breath respiratory gas exchange measurements were recorded throughout the test and averaged over a peak width of 20 s at the end of exercise to determine maximum values. Patients were encouraged to exercise until exhaustion.

CMR was performed immediately before invasive catheterization. All scans were performed on an Intera 1.5-T scanner (Koninklijke Philips N.V., Amsterdam, the Netherlands).

The CMR protocol consisted of cine-sequences, T_1-weighted spin-echo, and 2-dimensional inversion recovery gradient echo sequences for late enhancement assessment after gadobutrol administration.

T_1 mapping was performed with a modified Look-Locker inversion recovery sequence with a 3(3)5 scheme before and 15 min after contrast application (22). Mapping was performed over all available short-axis slices. ECV was calculated on the basis of the combination of pre- and post-contrast T_1

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