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Focal fibrosis and diffuse fibrosis are predictors of reversed left ventricular remodeling in patients with non-ischemic cardiomyopathy

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ABSTRACT

Background: Prognostic value of myocardial fibrosis in patients with non-ischemic idiopathic dilated cardiomyopathy (DCM) is not well-defined. We sought to assess the association of focal and diffuse myocardial fibrosis with left ventricular reversed remodeling (LVRR).

Methods: Patients with DCM who underwent cardiac MRI with baseline and subsequent follow-up echocardiography were included in the study. Post-contrast T1 times were corrected for renal function, body size, gadolinium dose and time after Gadolinium injection. Patients were followed over a median time of 29 months to evaluate changes of left ventricular end-systolic volume (LVESV). A Linear Mixed Model was used to assess the relationship between the LVESV during follow-up, corrected post-T1 value delayed hyperenhancement (DHE), and modified Seattle Heart Failure Score (SHFS).

Results: A total of 103 patients (mean age 51 ± 15 years, 61% male) were evaluated. The mean LVEF was 33 ± 11%, LVESVi 62 ± 39 ml/m^2, and T1 time 416 ± 98. DHE was identified in 45 patients (44%). Patients with focal DHE (n = 45) had higher LVESVi at baseline and during follow-up (p = 0.024). Post T1 value >450 was an independent predictor of LVRR at the follow-up (Δ = 24.6 ml/m^2 SE 14.6 ml/2, p = 0.0480) in patients despite the presence of DHE, even after adjusting for their SHFS.

Conclusion: While DCM patients with focal DHE demonstrated greater adverse LV remodeling than those without focal fibrosis, diffuse fibrosis independently predicts LVRR in DCM patients in patients despite the presence of focal fibrosis.

1. Introduction

Idiopathic dilated cardiomyopathy (DCM) affects over 100,000 patients in the Unites States and is the most common cause of heart failure in young adults who are referred for heart transplantation [1,2]. Although many of these patients progress to end stage heart failure, up to 37% of these patients experience reverse remodeling (LVRR), defined as improvement in left ventricular ejection fraction (LVEF) and decrease in left ventricular volume. This has been identified as an independent predictor of better prognostic outcome in patients with dilated cardiomyopathy [3]. Therefore, prediction of LVRR would be important not only for risk stratification but also for optimal timing of implantable cardioverter-defibrillators and consideration of advanced heart failure therapy, such as ventricular assist devices and cardiac transplantation.

Focal replacement fibrosis, identified by delayed hyperenhancement (DHE), is an important prognostic finding and is associated with progressive LV remodeling and poor outcomes in patients with DCM [4,5]. However, DHE does not provide quantification and assessment of diffuse myocardial fibrosis, which is frequently present in patients DCM [6]. The role of identifying and quantifying focal and diffuse myocardial fibrosis in the prediction of LVRR, after controlling for clinical variables, has not been clearly elucidated. T1 mapping has been shown to be a marker of diffuse fibrosis with significant histopathological correlation [7,8]. We sought to identify the role of focal fibrosis as detected by delayed enhancement imaging and diffuse fibrosis as indicated by T1 mapping to predict LVRR in patients with idiopathic DCM.

2. Methods

2.1. Study population

This was an observational cohort study of consecutive patients with idiopathic non-ischemic cardiomyopathy who underwent echocardiography and cardiac MRI at the Cleveland Clinic between January 2008 and January 2013. Idiopathic non-ischemic cardiomyopathy was

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defined as LVEF <50% in the absence of coronary artery disease by coronary angiography or coronary computed tomography). Patients were excluded if they had significant valvular heart disease, history of drug or alcohol abuse, persistent supraventricular tachyarrhythmias, systemic disorders with associated cardiomyopathy including cardiac hemochromatosis, cardiac sarcoidosis, cardiac amyloidosis, or incomplete follow-up data.

2.2. Study protocol

At baseline, all subjects underwent a clinical assessment, electrocardiography, echocardiography and CMR. Demographic information included self-designated race (white, black Asia, or other), anti-heart failure medications and device therapy was collected. These baseline clinical parameters were included into the modified Seattle-Heart Failure Risk Model.

2.3. Modified Seattle Heart Failure Score (MSHFS)

Modification of the Seattle Heart Failure Score was used as previously described [9]. Variables including age, gender, ischemic origin, systolic blood pressure, ejection fraction, medication use (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, statin, and daily diuretic dose), and serum sodium were used to calculate the MSHFS. Data on allopurinol use, total cholesterol, hemoglobin, percent lymphocytes, or uric acid were not available.

2.4. Echocardiography

Baseline transthoracic echocardiography was performed within 1 month of the baseline CMR. All patients returned for follow-up echocardiograms at least 6 months from the time of CMR by experienced sonographers using a commercially available ultrasound machines (Vivid 9, GE Vingmed Ultrasound AS, Horten, Norway; iE33, Philips Medical Systems, Andovers, Massachusetts). The median follow-up time was 29 months (20,37). All echocardiograms that were obtained during the follow-up time were included in our study. 2DE images were obtained from the apical 4- and 2- chamber views. Endocardial contours were traced manually, including the papillary muscles in the LV cavity, according to the American Society of Echocardiography guideline [10]. The traced contours were then used to calculate LV volume and LV ejection fraction using Simpson's formula.

2.5. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) was performed on Achieva 1.5 T Scanner (Philips Medical systems. Best, The Netherlands), using 40–45 mT/m maximum gradient strength, 200 T/m/s maximum slew rate) with electrocardiographic gating. For assessment of global cardiac function, balanced steady-state free precession (bSSFP) images were acquired (echo time 1.6 ms, repetition time 3.3 ms, flip angle 70°, and slice thickness 8–10 mm in contiguous short-axis images. For short-axis images, the spatial resolution was 1.5–2.1 mm (x-direction) × 1.1–1.1–1.4 mm (y-direction). LV volumes and LVEF were calculated on the basis of short-axis bSSFP images. DHE-CMR images were obtained in long and short-axis orientations as the bSSFP images, approximately 8–20 min after injection of 0.2 mmol/kg of Gadolinium dimenglumine (Magnevist, Berlex Imaging, Wayne, New Jersey), with phase-sensitive inversion recovery spoiled gradient echo sequence: echocardiography time 4 ms, repetition time 8 ms, flip angle 30°, and spatial resolution of 1.5–2.1 mm (x-direction) by 1.1–1.4 mm (y-direction).

LVEF and LV volume were analyzed on Philips workstation with Extended MR Workspace software. (Philips, Best, The Natherlands). LVEF was calculated using multi-slice disk summation techniques.

2.6. Delayed hyperenhancement (DHE) CMR

Phase sensitive inversion recovery DHE imaging was performed following the intravenous injection of Gd-diethylenetriamine penta-acetic acid (0.2 mmol/kg body weight), using an inversion-recovery spoiled gradient-echo technique in the cardiac short-axis, vertical long axis as well as 3- and 4- chamber long-axis planes. Inversion time was selected for optimal nulling of viable myocardium based on evaluation of images obtained from an ultrafast gradient-echo pulse sequence (Look-Locker technique), using a single short-axis slice with progressively increasing inversion time. Post-Gd images were obtained 10–20 min following Gd injection. For each study, the presence and absence of myocardial DHE was assessed by level 3 CMR readers.

2.7. T-1 mapping

T1 measurements were obtained from postcontrast Look-Locker inversion-recovery sequence using a balanced steady-state free-precession sequence obtained 9.1 min + 3.8 (SD) after contrast agent injection. Endo- and epicardial borders of the LV, excluding papillary muscle and areas of focal DHE, were traced semi-automatically in short-axis views in all phases of Look-Locker sequence. T1 values for individual pixels within the myocardium were determined by means of an iterative curve fitting technique using CVi42 Software (Calgary, Canada). T1 time was adjusted for renal function, body size, gadolinium dose and delayed time after Gadolinium injection.[11] T1 values were categorized into those with post-contrast values ≥450 msec, and those with post contrast T1 values <450 msec. The selection of 450 msec as the cut-point for post-contrast T1 values was based on the previously published normal values with the LL T1mapping method, which has been validated with histopathology [8].

2.8. Statistical analysis

Baseline demographic data, risk factors, and clinical variables were descriptively summarized with continuous variables expressed as mean ± SD and categorical data presented as percentage frequency. Differences between the groups were compared with the use of the Student *t* test for continuous variables and the chi-square test for categorical variables.

Linear mixed model regression was used to analyze the effect of T1 mapping and temporal trend of left ventricular ejection fraction and left ventricular end systolic volume. Both unadjusted and adjusted models were performed to assess the confounding effect of T1, Seattle Heart Failure Score and the presence of DHE. Subgroup analysis was performed in patients with DHE and those with global longitudinal strain (GLS) data, by linear mixed model controlling T1 time and SHFM. SAS version 9.3 (The SAS Institute Cary, NC) was used to perform all analysis. Interobserver and Intraobserver reproducibility were assessed using a 2-way ANOVA approach.

3. Results

3.1. Patient sample

Our initial population included 1103 patients who underwent cardiac MRI due to suspected cardiomyopathy. Of these, 153 patients met criteria for the diagnosis of idiopathic DCM. There were 51 patients who had incomplete follow-up echo data, and were excluded.

A total of 103 patients who underwent CMR and echocardiography with subsequent follow-up echocardiograms were included in the analysis. The time difference between the baseline echocardiography and baseline CMR was 7 ± 9 days (ranges 0 to30). Our study population was predominantly male (60.8%), with a mean age of 50.6 ± 15.2 years. The patients in our study had moderate LV systolic dysfunction with mild LV dilation (mean LVEF of 33 ± 11% and LVEDVi of 90 ±