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Left ventricular remodeling and fibrosis: Sex differences and relationship with diastolic function in hypertrophic cardiomyopathy

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ABSTRACT

Objectives: We investigated sex differences in left ventricular (LV) remodeling and fibrosis and their relationship with LV diastolic dysfunction by cardiovascular magnetic resonance (CMR).
Methods: CMR imaging was performed simultaneously in 152 age-matched patients (76 men, 76 women; mean age: 49 ± 9 years) without LV systolic dysfunction. LV remodeling index (LVRI) was calculated as the ratio of LV mass and end-diastolic volume. Diastolic function indexes including peak filling rate (PFR) and time to PFR (tPFR) were evaluated. Extent of late gadolinium enhancement (LGE) was measured.
Results: LVRI and extent of LGE were greater in women compared with men (1.48 ± 0.22 vs. 1.36 ± 0.28 g/ml; 13.15 ± 2.48 vs. 11.35 ± 2.34 g, respectively, both $P < 0.001$). Women had lower PFR and higher tPFR (both $P < 0.001$) than men. LVRI and the extent of LGE showed significant relationships with parameters of diastolic function in both sex. In a multivariate analysis, LVRI remained a strong independent predictor of PFR and TPFR in women ($\beta = -0.272$, $P = 0.032$; $\beta = 0.348$, $P = 0.016$, respectively), and in men ($\beta = -0.374$, $P < 0.001$; $\beta = 0.660$, $P < 0.001$, respectively). Furthermore, the extent of LGE also remained an independent predictor of PFR in women ($\beta = -0.283$, $P = 0.033$) and men ($\beta = -0.492$, $P < 0.001$).
Conclusions: There are prominent sex differences in LV remodeling and myocardial fibrosis. We suggest that the effects of LV remodeling and fibrosis may lead to diastolic dysfunction with greater susceptibility to worse clinical outcome in women.

1. Introduction

Myocardial remodeling is defined as the changes in shape, dimension, and function of cardiac chambers after the myocardium suffer from an injury (i.e., necrosis, pressure overload, volume overload) [1]. Sex has a profound impact on cardiac remodeling and the remodeling process appears to be more favorable in women in specific pathophysiological settings including diastolic heart failure, chronic pressure overload, myocardial ischemia and obesity [2–6].

Hypertrophic cardiomyopathy (HCM) is characterized by ventricular hypertrophy, myocardial fibrosis, and impaired diastolic function, and is often linked with a high incidence of sudden cardiac death [7]. Recent studies showed that sex was also associated with severity and prognosis in HCM patients, and women were more likely to present with heart failure and death [8–10]. The myocardial remodeling and fibrosis are known to affect diastolic function in HCM, which may contribute to the greater predisposition to heart failure in women compared with men [10–12]. To our knowledge, there are few studies to elucidate gender-related differences in left ventricular (LV) remodeling and fibrosis and their impact on diastolic function.

Cardiovascular magnetic resonance (CMR) can accurately assess LV mass and volume with high intra- and inter-observer reproducibility [13]. Late gadolinium enhancement (LGE) can quantitatively evaluate extent of myocardial fibrosis [14]. Therefore, we aimed to investigate sex differences in LV remodeling and fibrosis and relationship with diastolic function between men and women with HCM.

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2. Methods

2.1. Patients

The study period extended from August 2008 to December 2012. Patients with prior surgical myectomy, aortic valvular disease, intrinsic mitral disease, left ventricular ejection fraction <50%, and pacemaker dependency as well as the general contraindications for CMR were excluded from the study. Finally, 152 patients with HCM referred for CMR as part of clinical evaluation were evaluated (76 women, mean age 49 ± 9 years; 76 men mean age 50 ± 9 years). The diagnosis of HCM was based on typical clinical, electrocardiographic, and echocardiographic features, with ventricular myocardial hypertrophy occurring in the absence of any other cardiac or systemic diseases. Obstructive HCM was defined left ventricular outflow tract (LVOT) gradient either ≥40 mm Hg at rest and/or ≥50 mm Hg during provocation used Doppler echocardiography [15]. The study protocol was approved by the Institutional Ethics Committee of Fuwai Hospital.

2.2. Image acquisition

CMR imaging was performed in all patients. All scans were performed using a 1.5-T speed clinical scanner (Siemens Medical Solutions, Erlangen, Germany). Scout images were obtained initially to identify the cardiac axes. To evaluate functional parameters, electrocardiographic gating cine images were then acquired using a segmented, balanced, steady state free precession sequence. The images were acquired during multiple short breath holds (8 to 15 s). After scout images, cine imaging was performed in four-chamber, three-chamber and two-chamber long- and short-axis views with the following protocol: repetition time (TR), 2.7 ms; echo time (TE), 1.2 ms; flip angle, 70°; temporal resolution, 40 ms; field of view (FOV), 360 × 315 mm^2; matrix, 192 × 162; 6-mm-thick sections with a 2-mm gap between sections. The LGE images were obtained 10–15 min after intravenous administration of 0.2 mmol/kg gadolinium–diethylene triamine pentacetate acid (Magnevist, Schering AG, Berlin, Germany), using a segmented phase-sensitive inversion recovery (PISR) spoiled gradient echo sequence at the same position as the long- and short-axis cines in end diastole. Typical imaging parameters were: slice gap, 1.6 mm; pixel size, 2 × 1.5 mm^2; matrix, 256 × 162; FOV, 380 × 320 mm^2; flip angle, 25°; TR, 8.6 ms, TE, 3.36 ms. The inversion time was adjusted per patient to optimally null signal from normal myocardium typically between 250 and 350 ms. Total acquisition time averaged 45 min.

2.3. Image analysis

All MR image analysis was performed using the commercial software (Medis Medical Imaging systems, Netherlands) by a single experienced observer who was blinded to the patients' clinical and procedural data. CMR imaging studies were analyzed in all LV short-axis slices across all temporal phases (200–250 images). LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using the Simpson method and ejection fraction (EF) was calculated as (EDV − ESV)/EDV × 100. Basal image position was defined as the basal-most image encompassing at least 50% circumferential myocardium. Left ventricular mass (LVM) was obtained on the basis of end-diastolic endocardial and epicardial contours, and calculated as the product of myocardial volume and specific density of myocardial tissue (1.05 g/ml). LVM and LV EDV were indexed to body surface area, and left ventricular remodeling index (LVRI = LVM/LVEDV) was calculated used the methods described previously [16].

For assessment of left ventricular filling patterns, endocardial and epicardial contours were semi-automatically drawn and manually corrected. End-diastolic and end-systolic frames were identified according to the ventricular blood pool area excluding papillary and trabecular structures across all end diastolic temporal phases using short axis images from base to apex. The following CMR diastolic parameters were evaluated by previous methods [17]: Peak filling rate (PFR); representing the steepest tangent to the first part of the filling curve. Segment software automatically determines this parameter; normalized peak filling rate (nPFR) representing the PFR normalized for LV stroke volume; and the Time to peak filling rate (TPFR) defined as the time interval between end-systole and peak filling rate.

The presence of LV LGE was first assessed visually by 2 observers blinded to all patients details (Fig. 1). The extent of scarred myocardium was determined automatically by computer counting of all hyperenhanced pixels in the myocardium on each of the short-axis images. Hyperenhanced pixels resembling LGE were defined as those with image intensities of 3 SDs above the mean of image intensities in a remote myocardial region in the same image, which has been shown to provide the greatest accuracy for LGE quantification in HCM [14]. Summing the LGE mass of all slices yielded the total mass of LGE.

2.4. Statistical methods

Data were expressed as mean ± standard deviation. Differences between sex groups were compared with Student *t* test for continuous variables and by chi-square test for categorical variables. Pearson correlation analyses were performed to determine the associations between parameters of diastolic function with LVRI and LGE in both sexes. Multiple linear regression was used to determine the independence of correlations observed on simple linear regression, with all correlations with a *P* value <0.1 entered into multiple linear regression analysis. Statistical significance was defined as $P < 0.05$ for all comparisons. Statistical analysis was conducted using SPSS version 18.0 for windows (SPSS Inc, Chicago, Illinois).

3. Results

3.1. Characteristics of the study population

The comparison between men and women with regard to demographic and clinical characteristics is presented in Table 1. Mean age was not significantly different between men and women ($P = 0.558$). There was significant difference in NYHA between men and women (2.03 ± 0.77 vs. 2.43 ± 0.84, $P = 0.002$). The proportion of angina, dyspnea, syncope, hypertension and diabetes mellitus did not differ significantly between men and women. For the medications, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers seemed to be more frequent in women, but without statistical significance. Women had more severe mitral regurgitation ($P = 0.012$) and greater LVOT gradient than men (87.46 ± 32.18 vs. 78.46 ± 20.71 mm Hg, $P = 0.042$).

3.2. Sex differences in LV remodeling and myocardial fibrosis

Table 1 shows the comparison of CMR findings between the groups. Women had smaller LV end-diastolic dimensions ($P = 0.021$), LVEDV ($P < 0.001$) and LVEDV index ($P = 0.046$) than men. However, there were no significant sex differences in LV mass index ($P = 0.123$) although LV mass was significantly higher in men than women ($P = 0.009$). The LVRI was significantly higher in women than men (1.48 ± 0.22 vs. 1.36 ± 0.28 g/ml, $P = 0.002$). LGE