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Impaired left atrial systolic function and inter-atrial dyssynchrony may contribute to symptoms of heart failure with preserved left ventricular ejection fraction: A comprehensive assessment by echocardiography

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ABSTRACT

Aims: To assess LA diastolic and systolic function and atrial dyssynchrony in patients with heart failure with preserved ejection fraction (HFpEF) and to examine whether LA dysfunction and dyssynchrony account for the patients' symptoms of HFpEF.

Methods: Fifty-five patients with HFpEF, 31 asymptomatic patients with left ventricular diastolic dysfunction (LVDD) and 33 healthy individuals were enrolled in the study. The LA active ejection fraction (LAAEF) was calculated. The peak atrial longitudinal systolic strain (PALS) and peak atrial contraction strain (PACS) were measured using speckle tracking echocardiography (STE). Atrial dyssynchrony including inter-atrial dyssynchrony, LA dyssynchrony and right atrial dyssynchrony were calculated by tissue Doppler imaging (TDI).

Results: The PALS and PACS were deteriorated, whereas inter-atrial dyssynchrony was prolonged in patients with HFpEF (20.41 ± 7.41%, 10.83 ± 4.19%, 31 ± 15 ms, respectively) compared with the values obtained in asymptomatic LVDD patients (26.61 ± 6.30%, 13.23 ± 4.52%, 19 ± 12 ms, respectively) and those found in normal individuals (33.51 ± 6.74%, 14.17 ± 2.88%, 17 ± 12 ms, respectively) ($P < 0.05$). However, PACS and inter-atrial dyssynchrony did not reach statistical significance between asymptomatic LVDD and normal individuals ($P > 0.05$). Moreover, patients with deteriorated clinical symptoms (NYHA > II) presented worse LA systolic function and prolonged dyssynchrony compared with those with NYHA = II. Inter-atrial dyssynchrony and LAAEF are independently associated with worse NYHA functional classes in patients with HFpEF.

Conclusions: LA diastolic and systolic function were significantly impaired, and inter-atrial dyssynchrony was prolonged in patients with HFpEF. Decreased LA systolic function and prolonged inter-atrial dyssynchrony were possibly associated with deteriorated clinical symptoms.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) affects approximately half of the entire heart failure (HF) population and causes many hospitalizations, but there is currently no effective treatment [1]. As an unsolved problem, the underlying pathophysiological mechanisms of HFpEF remain poorly understood. It is well known that elevated left ventricular (LV) filling pressure is a main reason of advanced LV diastolic dysfunction (LVDD) [2]. The increased left atrial (LA) afterload in the development of elevated LV filling pressure has long been considered a major underlying etiology of LA remodeling and dysfunction [3–4]. Speckle tracking echocardiography (STE) has recently emerged as a robust technique to quantify LA strain in numerous cardiac disorders including hypertension, atrial fibrillation and diastolic heart failure [5–7]. The LA longitudinal systolic and diastolic dysfunction, as assessed by STE, are important factors that contribute to reduced functional capacity during effort in patients with HFpEF, as a recent study showed [4]. However, the degree of LA longitudinal systolic and diastolic dysfunction may not fully explain the patients' symptoms, and other reasons, such as atrial dyssynchrony, may play a role in the pathophysiology of HFpEF [8–9].

Inter-atrial dyssynchrony is associated with abnormal atrial excitability, which causes electrical remodeling and LV filling reduction [10]. As a potentially treatable condition, inter-atrial conduction delay, as measured by tissue Doppler imaging (TDI), may be related to significant cardiac morbidity and atrial arrhythmia [11–12]. However, there is

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a paucity of data providing a comprehensive assessment of LA diastolic and systolic function and its relationship with clinical symptoms in patients with HFpEF.

In the present study, we hypothesized that LA dysfunction and dyssynchrony were responsible for the symptoms of HF in the development of HFpEF. In this regard, we comprehensively assessed LA diastolic and systolic function, as well as dyssynchrony, in patients with HFpEF and investigated the relationship between LA performance and symptoms in patients with HFpEF.

2. Methods

2.1. Patient selection

Fifty-five consecutive patients (25 men and 30 women) with HFpEF from the First Hospital of China Medical University were enrolled in this study between January 2015 and January 2016. According to the diagnostic criteria of the American Society of Echocardiography, the following three conditions were necessary for a diagnosis of HFpEF: (1) signs or symptoms of congestive HF, including dyspnea (NYHA class ≥ II), fatigue, pulmonary rales, pulmonary edema, bilateral lower extremity edema, and hepatomegaly; (2) left ventricular ejection fraction (LVEF) > 50% by biplane Simpson's method; and (3) evidence of left ventricular diastolic dysfunction according to the American Society of Echocardiography [13]. Thus, 31 asymptomatic patients (16 men and 15 women) with LVDD were enrolled as the LVDD group. The diagnosis of LVDD was made according to the recommendations of the American Society of Echocardiography [13]. Patients under 18 years of age and those with valvular heart disease, conduction abnormalities, rhythm disturbances, cardiomyopathy, constrictive pericarditis, severe pulmonary disease, LV systolic dysfunction, other associated systemic diseases or poor echocardiographic view were excluded from the study.

Thirty-three healthy volunteers (12 men and 21 women) from the medical students and members of the local community who had neither abnormal echocardiographic findings nor symptoms of heart failure were randomly selected as normal controls (the control group), the age and gender are matched between control group and patient group. Written informed consent was obtained from all participants, and the study was approved by the ethics committee of China Medical University.

2.2. Echocardiography

While the participants were in the left lateral recumbent position, images were acquired using a Vivid 7 Dimension ultrasound system (GE Healthcare, Waukesha, WI, USA) equipped with a 2–4 MHz phased array probe. All images and measurements were acquired from standard views and were digitally stored for offline analysis. The LV diameters, volumes, mass of LV hypertrophy, LVEF, LA volume and remodeling, and LV diastolic function were measured according to the guidelines of the American Society of Echocardiography [14]. The LV end-diastolic pressure ($LVEDP_{echo}$) was estimated as $11.96 + 0.596 * E/e'$ [15].

2.3. LA data collection

The maximum LA volume (LAVmax), pre-atrial contraction LA volume (LAVpre-a), and minimum LA volume (LAVmin) were measured using the area-length method according to the guidelines of the American Society of Echocardiography [14]. The LA volume indices (LAVI) were calculated by dividing the LAV by the BSA. The LA function parameters, such as LA total emptying fraction (LATEF) and the LA active emptying fraction (LAAEF), were calculated using similar methods to those used in previous study [16].

For the LA 2D-STE analysis, dynamic 2-D ultrasound images of 3 cardiac cycles from apical four-chamber and two-chamber views were acquired using conventional ultrasound, with a frame rate of 57–72 fps. The images were analyzed using customized software within the EchoPAC work station (GE Healthcare). The endocardial boundary of the left atrium was delineated manually, and the software automatically drew the epicardial boundary. The widths of the regions of interest were adjusted manually to match the actual endocardial and epicardial boundaries. An automatically generated region of interest was divided into 6 segments. The LA peak longitudinal systolic strain (PALS) was calculated from the mean value of the peak systolic strain of all LA segments during LV systolic phase, and the peak atrial contraction strain (PACS) was measured just before the beginning of the late diastolic phase. The final strain parameters were the averages of the values obtained for the four-chamber and two-chamber views [4].

The assessment of the LA longitudinal strain was considered suboptimal when speckle tracking could not be obtained for the 12 myocardial segments or if values that were theoretically unlikely were obtained.

Tissue Doppler was used for the assessment of LA dyssynchrony because of its high temporal resolution, which allows accurate measurement of mechanical dyssynchrony [17]. The tissue Doppler velocities were obtained from the lateral and septal sides of the mitral annulus and the right ventricular (RV) tricuspid annulus. The inter-atrial dyssynchrony was defined as the time difference between the beginning of the late diastolic wave of the lateral mitral annulus and tricuspid annulus, and the intra-atrial dyssynchrony of LA (LA dyssynchrony) was defined as the time interval between the onset of the late diastolic wave in the lateral and septal mitral annulus, whereas the intra-atrial dyssynchrony of the right atria (RA dyssynchrony) was defined as the difference between the septal mitral annulus and tricuspid annulus [18]. The value of 35 ms was used to define significant inter-atrial dyssynchrony as a previous study reported [18]. All echocardiographic parameters were calculated as averages of three heart beats [19].

2.4. Statistical analysis

Statistical analysis was performed using the SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive data were summarized as the percentage frequency for categorical variables and as the mean ± SD for continuous variables. Continuous variables between two groups were analyzed with the unpaired Student's *t*-test or Mann-Whitney test, and categorical data were analyzed using the Fisher exact test or Chi-squared test, as appropriate. Differences between multi-groups were compared with one-way analysis of variance (one-way ANOVA) through Bonferroni correction or Kruskal-Wallis test, as appropriate. Pearson coefficient was used for correlation analysis. The overall performances of variables for discriminating HFpEF and LVDD were quantified with receiver-operating characteristic (ROC) curve and were compared using the method of DeLong. The multivariate logistic regression with the "Enter" method was performed for assessing independence associated with functional capacity. A 2-tailed $P < 0.05$ was considered statistically significant. Inter- and intra-observer variability was determined by calculating the coefficients of variation, which were calculated as the standard deviations of differences between repeated measurements divided by the average value of those measurements and expressed as percentages.

3. Results

3.1. LV characteristics

The comorbidities in patients with HFpEF and LVDD were characterized by the presence of hypertension, history of coronary heart diseases, obesity and type 2 diabetes. The plasma BNP in patients with HFpEF was significantly higher than those with LVDD.

Although there is no significant difference in LVEF among the 3 groups, we found an increased LVEDD and LVMI in patients with LVDD and HFpEF compared with the values found in the normal controls ($P < 0.05$). Moreover, the $LVEDP_{echo}$ and E/e′ were significantly increased while e′ of the mitral annulus was significantly decreased in patients with LVDD and HFpEF compared with the control group ($P < 0.05$). Compared with patients with LVDD, the septal e′ of the mitral annulus was significantly decreased in patients with HFpEF. Although E/e′ did not reach statistical significance, it tended to be higher in patients with HFpEF than that in patients with LVDD (Table 1).

3.2. LA comprehensive performance

The values for LA functions and dyssynchrony are summarized in Table 2. The LAVmax, LAVpre-a, LAVmin and LAVI were significantly increased in patients with HFpEF compared with the control group ($P < 0.05$). Although not statistically significant, the LAVI, LAVmax, LAVpre-a and LAVmin values tended to be higher in patients with HFpEF than in patients with LVDD. The LATEF in patients with HFpEF and LVDD was markedly reduced compared with normal controls ($P < 0.05$); however, the LAAEF in these groups was not significantly decreased compared with the control group.

The PALS was significantly reduced in patients with HFpEF and LVDD compared with the control group, and PALS was more impaired in patients with HFpEF compared with patients with LVDD ($P < 0.05$), which suggests that the diastolic function was markedly reduced in patients with HFpEF. Although PACS did not reach statistical significance between normal controls and patients with LVDD, it was significantly reduced in patients with HFpEF ($P < 0.05$), indicating that systolic function was significantly impaired in patients with HFpEF. Moreover, the inter-atrial dyssynchrony was significantly increased in patients with HFpEF compared with normal controls and patients with LVDD ($P < 0.05$) (Fig. 1).

The inter-atrial dyssynchrony and LA dyssynchrony were negatively correlated with PALS ($r = -0.402$ and -0.313, respectively, $P < 0.01$), and PACS ($r = -0.239$ and -0.249, respectively, $P < 0.05$). Moreover,