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ORIGINAL RESEARCH ARTICLE

Left ventricular geometry transition in hypertensive patients with heart failure with preserved ejection fraction

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) develops in response to hypertensive left ventricular (LV) hypertrophy and is associated with increased cardiovascular events. Although the progression to systolic heart failure is a known consequence of LV hypertrophy and HFpEF, few data are available on the LV geometry change and frequency of deterioration to systolic dysfunction in this population.

Methods and results We evaluated the baseline and follow-up characteristics in 680 patients with LV hypertrophy and HFpEF in this prospective cohort study. The primary endpoint was 5 year all-cause mortality. The changes of LV geometry and heart failure transition were analysed. Systolic dysfunction [left ventricular ejection fraction (LVEF) $<$ 50%] occurred in 182 patients (26.8%) during a 5 year follow-up. Patients with LVEF deterioration were associated with a lower survival rate. Beta-blocker prescription was a protective factor for preserved LVEF. And concentric LV geometry shifted to eccentric hypertrophy was uncommon (10.6%) during a 5 year follow-up.

Conclusions A quarter of patients with hypertensive LV hypertrophy and HFpEF progresses to systolic dysfunction during a 5 year follow-up, which was accompanied by poor clinical outcomes. And beta-blocker therapy might play a protective role for preserved LVEF in this population.

Keywords Hypertension; Left ventricular hypertrophy; Heart failure; Transition

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Introduction

Hypertension, due to its high prevalence, is the single greatest risk factor for heart failure (HF) at a population level. Hypertensive heart disease refers to the clinical manifestations of heart disease caused by the impact of hypertension on the heart, which includes the development of diastolic dysfunction, left ventricular (LV) hypertrophy, and heart failure with preserved ejection fraction (HFpEF).[1] A subset of these patients ultimately develops heart failure with mid-range ejection fraction (HFmrEF) or heart failure with reduced ejection fraction (HFrEF) owing to ischaemia, genetic polymorphisms, or other insults to the cardiac myocytes.[2] Compared with HFpEF, once HFmrEF/HFrEF develops due to LV ejection fraction (LVEF) deterioration, its prognosis becomes markedly worse.[3–5] Despite significant advances in therapy for systolic HF, the overall survival rate remains unsatisfactory.[3–5] Early screening and intervention are keys to preventing hypertensive patients from LV hypertrophy to HFpEF and then to HFmrEF/HFrEF. Even after the onset of HFpEF in patients with hypertensive LV hypertrophy, prompt initiation of therapy may still lead to the reversal of remodelling or preventing LVEF deterioration.[4]

Although it is postulated that over time, patients with HFpEF can progress to systolic dysfunction,[4] there are scant data describing the frequency and predictors of decompensation or a subsequent decrease in systolic function. Therefore, the purpose of this prospective cohort study was to describe

the frequency and associated risk factors for the development of LV systolic dysfunction in patients who presented with hypertensive LV hypertrophy and HFpEF. Finally, we assessed whether the clinical outcome was associated with different responses to guideline-directed medical therapies.

Methods

Study design and patient enrolment

Patients with HFpEF were derived from our prospective HF cohort study that has previously been described.[3,4,6] HFpEF was defined by clinical features of HF with LVEF greater than or equal to 50%.[7] Patients were those over age 18 years with a clinical diagnosis of HFpEF, according to the attending physician. Recruitment occurred either where the patient was in hospital for a primary diagnosis of HFpEF (assessment was performed following stabilization of the acute HF) or in the outpatient setting within 3 months of an episode of decompensated HF (requiring hospitalization or treatment in an outpatient setting). Inclusion criteria also composed of diagnosis of hypertension and echocardiographic signs of LV hypertrophy [LV mass index (LVMI) was >115 g/m^2 for men and >95 g/m^2 for women]. Patients enrolled in this study had echocardiographic data at baseline as well as at the end of follow-up. Exclusion criteria included severe valve disease, transient acute pulmonary oedema in the context of primary acute coronary syndrome, end-stage renal failure (estimated glomerular filtration rate $<$ 30 mL/min/1.73 m^2), specific HF subgroups (including constrictive pericarditis, congenital heart disease, hypertrophic cardiomyopathy, cardiac amyloid, and chemotherapy-associated cardiomyopathy), isolated right HF, and life-threatening co-morbidity with life expectancy $<$ 1 year. Besides, patients with initial LVEF $\leq$ 50%, but improved to $\geq$50% during the index admission period, were also excluded. All participants were informed of the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the institutional ethics committee.

Endpoints and follow-up

The primary outcome of this study was defined as 5 year all-cause mortality. Most of the patients visited our outpatient clinic at least every 3 months. However, if the patients did not appear at their scheduled clinic, they were interviewed by telephone annually. Information regarding the primary outcomes was documented in chart records and via telephone interviews. During the follow-up, we recorded the HF transition (HFpEF shifted to HFmrEF/HFrEF). According to current guidelines, eccentric hypertrophy was defined as LVMI $>$ 95 g/m^2 for women and $>$115 g/m^2 for men with a relative wall thickness (RWT) $\leq$ 0.42; concentric hypertrophy was defined as LVMI $>$ 95 g/m^2 for women and $>$115 g/m^2 for men with a RWT $>$ 0.42.

Statistical analysis

Statistical analysis was performed using SPSS Statistical Software, Version 22.0 (SPSS Inc., Chicago, IL, USA). Arithmetic means ± standard deviations were calculated for quantitative variables, while qualitative variables were given as frequency and percentage. For quantitative variable analysis, the *t*-test was used. A two-sided χ^2 test was used to compare qualitative variables. Differences in clinical endpoints between HF phenotype were tested with χ^2 test. Univariate and multivariate logistic regression analyses of relevant variables were performed to identify predictors for the HF transitions (HFpEF shifted to HFmrEF/HFrEF). Univariate and multivariate Cox proportional hazards regression model was used to explore the association between risk factors and all-cause mortality. All predictors with a significance of $P \leq 0.10$ in the univariate analysis were entered into the multivariable model. Odds ratios (ORs)/hazard ratios and corresponding 95% confidence intervals (CIs) were reported. Freedom from the occurrence of all-cause mortality at 5 years or LVEF deterioration was analysed with Kaplan–Meier statistics, with differences assessed using the log-rank test. All values were two-tailed, and a P value $<$ 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

There were 806 patients with a diagnosis of HFpEF and hypertensive LV hypertrophy in this prospective longitudinal cohort from January 2007 to December 2015, and 126 patients were excluded because of missing echocardiographic data, lost to follow-up, or other exclusion criteria. Of the 680 enrolled patients, 26.8% (n = 182) progressed to HFmrEF/HFrEF, and 73.2% (n = 498) remained HFpEF during 5 year follow-up. And 244 patients died during the follow-up, in which 78 patients were with an LVEF $<$ 50% and 166 patients with an LVEF $\geq$ 50%. Of the remaining 436 patients, whereby 104 patients were with an LVEF $<$ 50%, and 332 patients with an LVEF $\geq$ 50%. Compared with patients with HFpEF, those who transitioned to HFmrEF/HFrEF were older (mean age 70.8 vs. 69.6 years), more likely to have a history of ischaemic heart disease (37.4% vs. 27.5%) and type 2 diabetes mellitus (42.9% vs. 32.3%), and less often beta-blocker prescribed (53.3% vs. 63.1%). In regard to the echocardiographic findings, patients remained HFpEF phenotypes had higher levels

of LVEF and RWT. And the B-type natriuretic peptide (BNP) level in the HFmrEF/HFrEF group was higher than that in the HFpEF group (*Table 1*). The prevalence of concentric or eccentric hypertrophy was markedly different in the two groups. The eccentric hypertrophy was much often in the HFmrEF/HFrEF group. *Table 1* presents the clinical characteristics of patients with HFpEF or HFmrEF/HFrEF at the index admission.

Left ventricular ejection fraction change and heart failure transition

The results of univariate and multivariate logistic regression indicated that age (OR 1.041, 95% CI 1.007–1.075, P = 0.016), ischaemic heart disease (OR 1.548, 95% CI 1.041–2.301, P = 0.031), and BNP (OR 1.056, 95% CI 1.029–1.098, P = 0.018) were associated with an increased possibility of deteriorated HF transition (HFpEF shifted to HFmrEF/HFrEF), whereas the use of beta-blockers (OR 0.689, 95% CI 0.486–0.979, P = 0.037), higher LVEF level (OR 0.942, 95% CI 0.903–0.983, P = 0.006), and concentric hypertrophy (OR 0.148, 95% CI 0.1000–0.219, $P < 0.001$) were associated with a reduced possibility of deteriorated HF transition during the follow-up (*Table 2*). Subjects prescribed with beta-blockers also showed a reduced possibility of deteriorated HF transition in Kaplan–Meier plot (log-rank test, P = 0.009; *Figure 1*).

Besides, we also documented the new-onset acute coronary syndrome during the follow-up, which was more often in the HFmrEF/HFrEF group (19/182 vs. 21/498, P = 0.002). And 10.6% of patients with concentric phenotype transitioned to eccentric phenotype during the follow-up; the new-onset eccentric hypertrophy (transitioned from concentric hypertrophy) was much often in the HFmrEF/HFrEF group (21/182 vs. 25/498, P = 0.003).

Table 1 Baseline characteristics

	HFpEF (LVEF ≥ 50%)	HFrEF/HFmrEF (LVEF < 50%)	*P* value
n	498	182	
Age (years)	69.6 ± 6.5	70.8 ± 5.6	0.034
BMI	24.8 ± 2.2	25.1 ± 2.5	0.090
Women (gender)	232 (46.6)	71 (39.0)	0.078
Medical history			
Ischaemic heart disease	137 (27.5)	68 (37.4)	0.013
Prior PCI	76 (15.3)	36 (19.8)	0.160
Prior CABG	17 (3.4)	9 (4.9)	0.357
T2DM	161 (32.3)	78 (42.9)	0.011
Atrial fibrillation	189 (38.0)	60 (33.0)	0.232
Stroke	51 (10.2)	24 (13.2)	0.278
COPD	40 (8.0)	13 (7.1)	0.702
Smoking	39 (7.8)	126 (6.6)	0.297
Dyslipidaemia	45 (9.0)	139 (7.1)	0.408
Medications			
ACEI/ARB	350 (70.3)	131 (72.0)	0.667
Beta-blocker	314 (63.1)	97 (53.3)	0.021
Spironolactone	134 (26.9)	41 (22.5)	0.247
Anticoagulant	52 (10.4)	15 (8.2)	0.394
Antiplatelet	230 (46.2)	100 (54.9)	0.043
Statin	138 (27.7)	61 (33.5)	0.141
Clinical status			
NYHA class, in Classes I–IV	52/170/218/58	12/68/88/14	0.166
Laboratory variables			
eGFR (mL/min/1.73 m^2)	61.7 ± 10.0	61.9 ± 8.4	0.744
Haemoglobin (g/dL)	11.9 ± 1.6	11.9 ± 1.5	0.175
BNP (pg/mL)	695.3 ± 231.7	779.5 ± 405.6	0.001
Echo data			
LVEF (%)	59.8 ± 4.7	58.1 ± 4.6	<0.001
LAD (mm)	42.3 ± 3.7	42.4 ± 3.6	0.761
E/e'	13.1 ± 2.0	13.2 ± 2.1	0.695
LVMI (g/m^2)	144.3 ± 14.0	145.8 ± 13.2	0.190
RWT	0.46 ± 0.05	0.40 ± 0.05	<0.001
Concentric/eccentric hypertrophy	377/121	56/126	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; E/e', mitral Doppler early velocity/mitral annular early velocity; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; RWT, relative wall thickness; T2DM, type 2 diabetes mellitus.
Data are presented as mean ± standard deviation or number (%) of subjects.

Table 2 Multivariable logistic analysis for deteriorated heart failure transition

	OR	95% CI	*P* value
Age	1.041	1.007–1.075	0.016
T2DM	1.411	0.931–2.137	0.104
IHD	1.548	1.041–2.301	0.031
Atrial fibrillation	0.853	0.556–1.285	0.446
LVEF	0.942	0.903–0.983	0.006
LV geometry	0.148	0.100–0.219	<0.001
ACEI/ARB	0.978	0.636–1.653	0.919
Beta-blocker	0.689	0.486–0.979	0.037
Spironolactone	0.942	0.596–1.484	0.798
BNP category	1.056	1.029–1.098	0.018

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; IHD, ischaemic heart disease; LV geometry, left ventricular geometry (concentric or eccentric hypertrophy); LVEF, left ventricular ejection fraction; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Clinical outcomes

When compared with patients remained HFpEF phenotypes at the end, patients transitioned to HFmrEF/HFrEF had a higher all-cause mortality (42.9% vs. 33.3%, *P* = 0.022). Patients shifted to HFmrEF/HFrEF also showed a lower survival rate than those remained HFpEF in Kaplan–Meier plot (log-rank test, *P* = 0.024; *Figure 2*). In the multivariate Cox models, compared with the remaining HFpEF, transitioned to HFmrEF/HFrEF was associated with 33.3% increased risk of 5 year mortality (hazard ratio 1.333, 95% CI 1.012–1.757, *P* = 0.041), along with other significant factors: ischaemic heart disease, atrial fibrillation, and BNP level (*Table 3*).

Discussion

Hypertensive heart disease includes the development of diastolic dysfunction, LV hypertrophy, HFpEF, and HFrEF.[1,2] An instigating factor, such as an ischaemic event or coronary microvascular dysfunction, can cause HFpEF to progress to HFmrEF/HFrEF, which might be accompanied by the transition from concentric hypertrophy to eccentric hypertrophy or degenerating to a dilated heart with systolic dysfunction.[8]

Previous studies indicated that a lower ratio of patients with LV hypertrophy progressed to eccentric hypertrophy and HFrEF.[9–11] The Cardiovascular Health Study reported the natural history of individuals with LV hypertrophy and found that only 7% transitioned to eccentric hypertrophy

Figure 1 Kaplan–Meier curves of freedom from heart failure with preserved ejection fraction (HFpEF) shifted to heart failure with mid-range ejection fraction (HFmrEF)/heart failure with reduced ejection fraction (HFrEF). The numbers at the bottom of the figure are 'number at risk'.

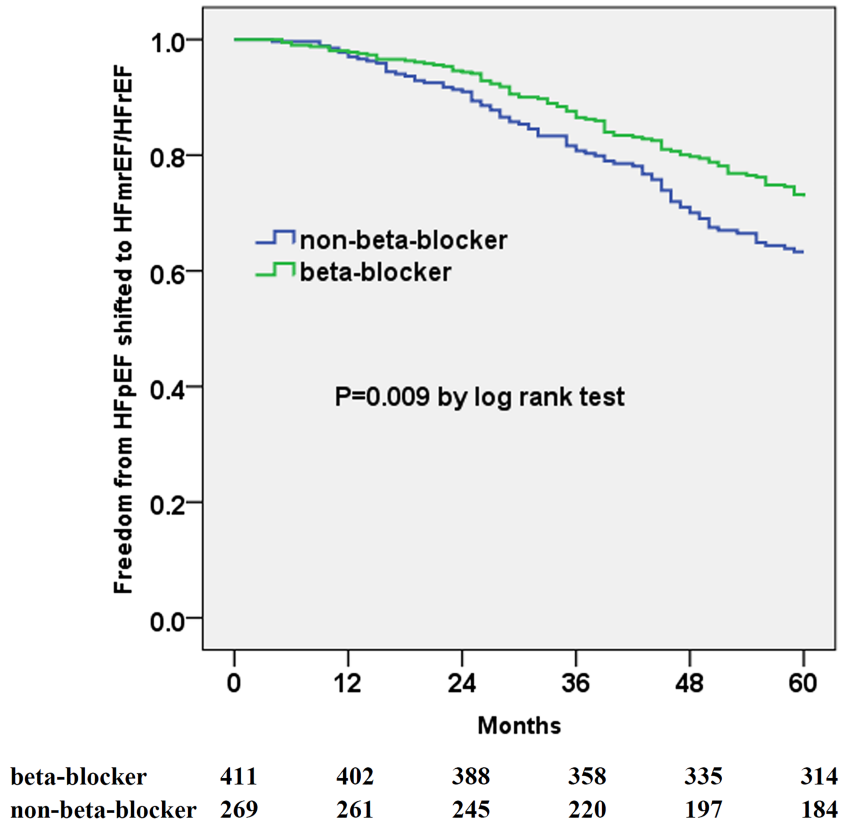

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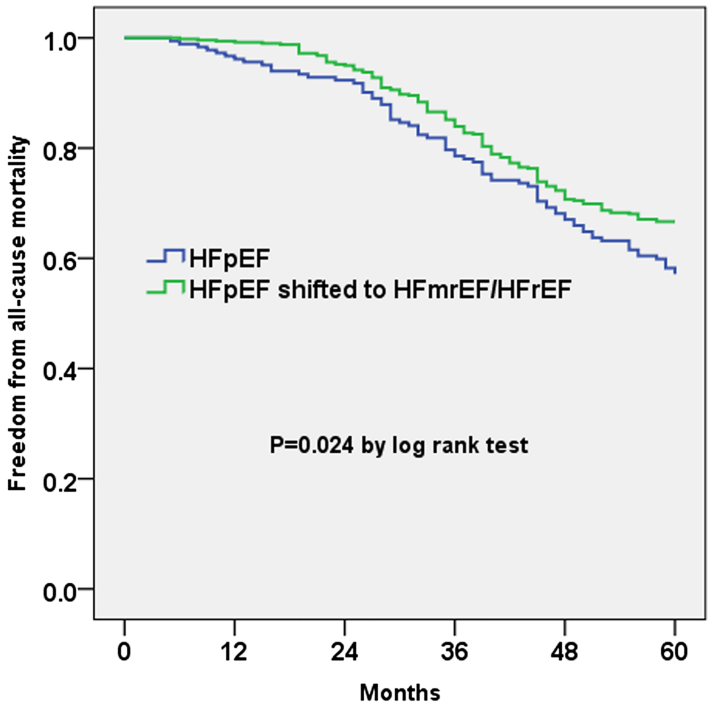
Figure 2 Kaplan–Meier curves of freedom from all-cause mortality. The numbers at the bottom of the figure are 'number at risk'. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



HFpEF	498	494	473	418	352	332
HFmrEF/HFrEF	182	175	168	143	122	104

Table 3 Multivariable Cox analysis for all-cause mortality

	HR	95% CI	*P* value
Age	1.007	0.986–1.208	0.535
T2DM	1.265	0.967–1.655	0.086
IHD	1.308	1.012–1.692	0.040
Atrial fibrillation	1.501	1.162–1.937	0.002
LVEF	1.019	0.992–1.047	0.176
LV geometry	0.207	0.014–3.074	0.253
E/e'	1.043	0.980–1.111	0.188
ACEI/ARB	0.938	0.711–1.236	0.648
Beta-blocker	0.813	0.630–1.051	0.114
Spironolactone	0.798	0.589–1.080	0.144
BNP category	1.178	1.003–1.383	0.046
HF transition	1.333	1.012–1.757	0.041

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; E/e', mitral Doppler early velocity/mitral annular early velocity; HF, heart failure; IHD, ischaemic heart disease; LV geometry, left ventricular geometry (eccentric or concentric hypertrophy); LVEF, left ventricular ejection fraction; OR, odds ratio; T2DM, type 2 diabetes mellitus.

over a 7 year period.[9] The development of eccentric hypertrophy was associated with a previous myocardial infarction or significant above-median LV mass.[9] A small study of patients with LV hypertrophy and a normal LVEF found that 18% eventually presented with a reduced LVEF after a median follow-up of approximately 4 years with a coronary event as the common precipitating cause.[10] Another study also showed that only 13% of patients with a normal LVEF and concentric LV hypertrophy progressed to systolic dysfunction during approximately 3 years of follow-up.[11] The risk factors for loss of function were interval myocardial infarction, prolonged QRS, and chronically elevated arterial impedance.[12] Coronary artery disease was also common in patients with HFpEF and was the predominant risk factor for disease progression and increased mortality.[12]

Previous studies focused on the transition from concentric LV hypertrophy without HF or with a normal LVEF to a depressed LVEF.[9–11] In this study, we enrolled patients with hypertensive LV hypertrophy and HFpEF and followed them for the risk of developing HFmrEF/HFrEF. The results indicated that nearly 27% of 680 subjects developed a reduced LVEF (<50%) during 5 years of follow-up. Just as the previous studies,[9–11] both a baseline history of ischaemic heart disease and a new-onset acute coronary syndrome were associated with the decreased LVEF. Moreover, in contrast, those who developed a reduced LVEF during follow-up had a lower LVEF and a smaller RWT or higher prevalence of eccentric

hypertrophy at baseline versus those who did not develop a reduced LVEF in the present study. Another study also indicated that eccentric hypertrophy was associated with reduced LV contractility and decreased LVEF compared with concentric hypertrophy after adjustment for covariates.[13] These data suggested that the differences in LV volume and geometry at baseline were associated with the LVEF change or HF transition.

In our enrolled subjects, the majority (73.2%) still had a preserved LVEF after given the long duration of follow-up. Furthermore, even among those with concentric LV hypertrophy at baseline who developed a reduced LVEF during follow-up, the LV geometry (62.5%) remained of a concentric phenotype. And overall, only 10.6% of patients with concentric phenotype transitioned to eccentric phenotype. Such findings suggested that patients with concentric LV hypertrophy might not frequently develop a dilated, thin-walled left ventricle. Our results were consistent with previous studies.[9–11]

Conventional medical treatments for HF [angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB), beta-blockers, and spironolactone] did not improve clinical outcomes for patients with hypertensive LV hypertrophy and HFpEF in the current study. However, it was indicated that beta-blockers might be favourable for decreasing the probability of HFpEF transition to HFmrEF/HFrEF. Our previous study showed that beta-blockers or spironolactone treatments could reduce LV mass, improve diastolic function, and reduce the incidence of HFpEF in patients with hypertension.[14,15] Some studies have indicated that once clinical HFpEF has manifested, there is minimal hope for reversing the disease process, and therapeutic options for HFpEF remain limited.[7,16] Until now, no medical intervention has been shown to alter mortality in HFpEF, and very few medications appear to alter the disease process at all.[7,16] As we previously described,[6] HFpEF was a heterogeneous syndrome; machine-learning-based clustering strategy was used to identify three distinct phenogroups of HFpEF that were characterized by significant differences in co-morbidity burden, underlying cardiac abnormalities, and long-term prognosis; and beta-blockers or ACEI/ARB therapy was associated with a lower risk of adverse events in specific phenogroup.[6] Moreover, our recent prospective longitudinal cohort study[4] examined the HF transitions over time and their clinical characteristics, prognosis, and response to medical therapy. And the result also indicated that (i) there were important LVEF transitions among HFpEF, HFmrEF, and HFrEF, especially during the first year; (ii) compared with patients with HF with unchanged ejection fraction (EF), patients with HF with improved EF showed lower mortality, whereas patients with HF with deteriorated EF manifested higher mortality; and (iii) beta-blocker was associated with an improved HF transition as well as a lower all-cause mortality in both HF with improved EF and HF with unchanged EF. Therefore, we speculated that beta-blockers might be beneficial for specific HFpEF phenotype, such as HFpEF derived from hypertensive LV hypertrophy in the present study. Compared with our previous study,[4] our present study investigated the HF transition and medical response and evaluated the LV geometry changes in patients with hypertensive LV hypertrophy and HFpEF during long-term follow-up.

A recent study[17] also evaluated the incidence, predictors, and associations with outcomes of changes in LVEF in patients with HF. Increases in LVEF occurred in one-fourth of patients with HFrEF and HFmrEF, and decreases occurred in more than one-third of patients with HFpEF and HFmrEF. LVEF change was associated with a wide range of important clinical factors as well as with outcomes, particularly transitions to and from HFrEF. Increased LVEF was associated with a lower risk and decreased LVEF with a higher risk of mortality and/or HF hospitalizations. Likewise, another study[18] determined whether the risk of clinical events experienced by patients with HFmrEF varies according to whether LVEF improved or deteriorated into the range of 40–50% from previous measurements. Patients whose LVEF deteriorated into mid-range levels experienced a significantly higher risk of adverse clinical events than patients whose LVEF had improved.

Limitations

Firstly, this prospective cohort study was not designed to specifically evaluate the transition of HF phenotype or LV geometry, and the sample size was too small to provide definitive results. The prescription of beta-blockers, ACEI/ARB, or spironolactone was left at the discretion of the responsible physicians, and the risk factors were not equally distributed among the groups. Therefore, a larger prospective cohort or a randomized-controlled study is necessary to understand the characteristics and evaluate the effects of drugs in this specific population. Secondly, the variability of LVEF determination could not be entirely averted during our long-term follow-up; however, all echocardiography tests were performed at a single echocardiography laboratory, which had followed strict standards of practice such that an LVEF assessment likely had high internal validity. According to our internal statistics, the variation in measurements between the two investigators was 3.5%. Lastly, the study participants were from a single centre in China, and it is uncertain whether these findings can be generalized to other ethnic groups.

Conclusions

The current study demonstrated the natural history of hypertensive LV hypertrophy and HFpEF. Nearly a quarter of those with HFpEF developed HFmrEF/HFrEF during a 5 year follow-up, which was associated with a poor clinical prognosis. Only a small minority of patients with concentric remodelling

developed eccentric hypertrophy, and prior ischaemic heart disease and baseline LV geometry were significant independent predictors of this transition. Besides, beta-blockers prescription might be favourable for the preserved LVEF in this population.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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