Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Transition From Asymptomatic Diastolic Dysfunction to Heart Failure With Preserved Ejection Fraction

– Roles of Systolic Function and Ventricular Distensibility –

Yoshihiro Aizawa, MD; Yasushi Sakata, MD; Toshiaki Mano, MD; Yasuharu Takeda, MD; Tomohito Ohtani, MD; Shunsuke Tamaki, MD; Yosuke Omori, MD; Yasumasa Tsukamoto, MD; Atsushi Hirayama, MD; Issei Komuro, MD; Kazuhiro Yamamoto, MD, PhD

Background: Systolic abnormality, as well as diastolic dysfunction, is observed in patients with heart failure with preserved ejection fraction (HFPEF). However, the role of these 2 conditions in the transition from asymptomatic diastolic dysfunction to symptomatic heart failure remains unclear. We recently demonstrated that diastolic wall strain (DWS) inversely correlates to the myocardial stiffness constant.

Methods and Results: This study consisted of 127 subjects: 52 consecutive HFPEF patients (HFPEF group), 50 asymptomatic hypertensive patients with ejection fraction ≥50% whose age, gender and left ventricular (LV) mass index matched those of the HFPEF group (HT group) and 25 normal volunteers (Normal group). The tissue Doppler-derived peak systolic and early diastolic velocities of the mitral annulus were significantly decreased in groups HFPEF and HT than in group Normal, but were not significantly different between groups HFPEF and HT. DWS was significantly lower in group HFPEF than in group HT.

Conclusions: The transition from asymptomatic diastolic dysfunction stage to HFPEF stage is not attributed to progression of systolic abnormality, and exacerbation of LV distensibility rather than relaxation plays a crucial role in the development of HFPEF. (*Circ J* 2011; **75:** 596–602)

Key Words: Diastole; Heart failure; Systole

In the past 2 decades, the prevalence of heart failure with preserved ejection fraction (HFPEF) has increased, and its prognosis is poor.[1,2] Left ventricular (LV) diastolic dysfunction proven by invasive assessment is present in most patients with HFPEF,[3,4] and has been implicated as a major factor responsible for the clinical syndromes of this phenotype of HF.

Several clinical studies have shown that there is systolic as well as diastolic dysfunction in patients with HFPEF,[5–8] and there has been a suspicion that the systolic dysfunction is responsible for the symptoms of HFPEF patients. However, the previous studies compared HFPEF patients to normal subjects. There are many asymptomatic patients with diastolic dysfunction,[9] and a comparison between patients with asymptomatic diastolic dysfunction and those with HFPEF is desirable to address the issue of the contribution of systolic dysfunction to the symptoms of HFPEF.

LV relaxation and compliance/distensibility are principal components of diastolic function.[10] Our previous experimental study demonstrated that the transition from the compensatory LV hypertrophic stage to HFPEF in the hypertensive heart was associated with an increase in the myocardial stiffness constant and a lack of the further change in the time constant of LV relaxation.[11] To clinically clarify the contribution of diastolic dysfunction to the incidence of HFPEF, LV relaxation and compliance/distensibility should be assessed respectively. Tissue Doppler imaging (TDI) of the mitral annulus level is widely used for noninvasive detection of diastolic dysfunction, but principally reflects LV relaxation.[12] Another noninvasive index of LV diastolic dysfunction is elevation of the LV filling pressure secondary to diastolic dysfunction.[10] Recently, we reported that LV distensibility can be evaluated noninvasively by echocardiography.[13]

The aim of this study was to investigate the contribution of

Received October 11, 2010; revised manuscript received October 29, 2010; accepted November 12, 2010; released online January 27, 2011 Time for primary review: 9 days

Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita (Y.A., Y.S., T.M., Y. Takeda, T.O., S.T., Y.O., Y. Tsukamoto, I.K., K.Y.); Division of Cardiology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo (Y.A., A.H.); and The Center for Advanced Medical Engineering and Informatics, Osaka University, Suita (S.T., K.Y.), Japan

Mailing address: Kazuhiro Yamamoto, MD, PhD, FACC, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan. E-mail: kazuhiro@medone.med.osaka-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-10-1037

Table 1. Definition of Heart Failure

Major	Minor
Paroxysmal nocturnal dyspnea	Edema
Orthopnea	Night cough
Abnormal jugular venous distention	Dyspnea on exertion
Pulmonary rales	Hepatomegaly
Cardiomegaly	Pleural effusion
Pulmonary edema	Tachycardia (>120 beats/min)
Presence of a third heart sound	Weight loss ≥4.5 kg in 5 days
Central venous pressure >16 cmH_2O	(Considered a major criterion if it occurs during therapeutic interventions for heart failure)
Hepatojugular reflux	

A patient is considered to have heart failure if 2 major criteria are present or if 1 major and 2 minor criteria are present concurrently.

Table 2. Clinical Characteristics of All Subjects

	Group Normal	Group HT	Group HFPEF
n	25	50	52
Age (years)	43±17	64±11*	68±12*
Men (%)	56	58	50
Height (m)	1.65±0.10	1.59±0.10*	1.59±0.09*
Weight (kg)	61±11	60±12	60±16
Body mass index (kg/m^2)	22±3.3	23±3.1	24±4.9
Comorbidity			
HT (%)		100	65†
Diabetes mellitus (%)		20	26
Dyslipidemia (%)		30	33
Medication			
Diuretic (%)		28	55†
Calcium-channel blocker (%)		54	53
β-blocker (%)		26	41
Angiotensin-converting enzyme inhibitor (%)		16	20
Angiotensin receptor blocker (%)		68	55
Mineralocorticoid receptor blocker (%)		8	24†
Statin (%)		28	25
Heart rate (beats/min)	66±10	63±8	64±11
Systolic blood pressure (mmHg)	118±11	136±19*	135±22*
Diastolic blood pressure (mmHg)	69±9	72±9	69±14

Values are mean ± SD. *P<0.05 vs. Normal group, †P<0.05 vs. HT group.
HT, hypertension; HFPEF, heart failure with preserved ejection fraction.

LV systolic and diastolic dysfunction to the transition from asymptomatic stage to HFPEF.

Methods

Study Subjects

This study consisted of 127 subjects in 3 groups. Of consecutive subjects who underwent echocardiography in Osaka University Hospital between July 2006 and December 2008, 52 outpatients with HFPEF who met the following criteria were selected (HFPEF group): (1) echocardiographic confirmation of EF≥50%, (2) without known coronary artery disease, segmental wall motion abnormalities, congenital heart disease, severe valve disease, atrial fibrillation, pulmonary disease, active collagen disease or renal failure (serum creatinine concentration >2.5 mg/dl), (3) meeting modified Framingham criteria,[14] as previously described[15] (Table 1) and (4) clinically stable. Medical records were reviewed by cardiologists to assess each patient's characteristics.

Of consecutive subjects who underwent echocardiography in Osaka University Hospital between December 2007 and August 2008, we selected 50 asymptomatic outpatients with hypertension and EF≥50% whose age, gender and LV mass index matched with those of HFPEF group (HT group). Patients with known coronary artery disease, segmental wall motion abnormalities, congenital heart disease, severe valve disease, atrial fibrillation, pulmonary disease, active collagen disease or renal failure were excluded. We also included 25 consecutive normal volunteers without cardiac disease, hypertension, dyslipidemia or diabetes mellitus (Normal group).

This retrospective study was approved by the Osaka University Hospital Ethics Committee. The original data for the patients in the HFPEF and HT groups were obtained from clinical practice and were retrospectively analyzed. Thus, in

Table 3. Echocardiographic Data

	Group Normal	Group HT	Group HFPEF
LV ejection fraction (%)	66±7	67±6	64±8
Left atrial dimension (mm)	33±5	39±6*	43±7*,†
LV end-diastolic dimension (mm)	48±5	48±6	48±6
LV end-systolic dimension (mm)	30±3	30±4	31±6
Interventricular septal thickness at end-diastole (mm)	7±1	10±2*	11±3*
Interventricular septal thickness at end-systole (mm)	10±1	13±2*	13±3*
LV posterior wall thickness at end-diastole (mm)	7±1	9±1	9±2
LV posterior wall thickness at end-systole (mm)	13±2	15±2*	14±3†
LV mass index (g/m^2)	70±16	102±26*	105±42*
LV relative wall thickness	0.32±0.05	0.39±0.07*	0.39±0.09*
Tricuspid regurgitation peak gradient (mmHg)	15±3	21±5*	26±14*,†
Mitral E (cm/s)	70±19	63±15	66±21
Mitral A (cm/s)	52±16	75±14*	77±27*
Mitral E/A ratio	1.5±0.5	0.9±0.2*	1.0±0.6*
Deceleration time of E wave (ms)	182±32	205±40	221±65*
Isovolumic relaxation time (ms)	67±14	72±17	77±25
E' (cm/s)	9.6±2.6	5.9±1.5*	5.5±1.7*
A' (cm/s)	8.7±1.7	9.1±1.7	8.3±2.1†
E/E' ratio	6.6±1.4	9.0±2.4*	11.9±4.5*,†

Values are mean±SD, *P<0.05 vs. Normal group, †P<0.05 vs. HT group.
LV, left ventricular; E/A, ratio of peak mitral E wave velocity to peak mitral A wave velocity; A', peak late diastolic myocardial velocity at septal position recorded by tissue Doppler imaging; E/E', ratio of peak mitral E wave velocity to peak early diastolic myocardial velocity at septal position recorded by tissue Doppler imaging. Other abbreviations see in Table 2.

compliance with the guiding principles of the Ministry of Health, Labour and Welfare, Japan, with regard to epidemiological study, the Ethics Committee approved data collection without the written informed consent of each patient. The normal volunteers gave written informed consent.

Data Collection

Echocardiographic recordings were obtained in all patients using commercially available machines and EF, relative wall thickness and LV mass were calculated as previously described.[13,16,17] EF was calculated by a modification of the method of Quinones et al.[18] The LV mass index was calculated as a ratio of LV mass to body surface area.[13,16] The right ventricular to right atrial pressure gradient during systole (tricuspid regurgitation peak gradient) was approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s. Transmitral flow velocity curves were recorded to measure peak early diastolic (E) and late diastolic (A) velocities.[16] TDI of the mitral annulus level was obtained at the septal position in order to measure the early diastolic (E'), late diastolic (A') and systolic (S') myocardial velocities as previously described.[13,17] Systolic function was assessed with S',[19–21] and LV relaxation was assessed with E'.[12] From our recent study, we reported that diastolic wall strain (DWS defined as follows) theoretically reflects LV distensibility according to linear elastic theory and was significantly and inversely correlated with myocardial stiffness constant in an animal HFPEF model.[13] Thus, we used DWS as an index of LV distensibility.

DWS=(LV posterior wall thickness at end-systole−LV posterior wall thickness at end-diastole)/LV posterior wall thickness at end-systole.

Statistical Analysis

Results are expressed as mean±SD. All statistical analyses were performed using commercially available statistical software (STATVIEW version 5.0, SAS Institute Inc, Cary, NC, USA). Differences between 2 groups were assessed using Student's t-test. Comparisons of nonparametric data were performed by chi-square test. Differences among 3 groups were assessed using 1-way analysis of variance followed by Fisher's protected least significant difference test. Correlations of 2 indices were assessed using linear regression analysis with the least-square method. P<0.05 was considered statistically significant.

Results

The characteristics of the study subjects are summarized in Table 2. Age and systolic blood pressure were higher in the HT and HFPEF groups than in the Normal group, and did not differ between the 2 groups. The prevalence of hypertension was less in the HFPEF group than in the HT group, but that of diabetes mellitus or dyslipidemia was not different between the 2 groups. Diuretic and mineralocorticoid receptor blocker were prescribed in more patients of the HFPEF group than of the HT group.

Echocardiographic data are summarized in Table 3. There was no difference in LV end-diastolic dimension or EF among the 3 groups. The E/A ratio and E' were lower, and the LV mass index and relative wall thickness were higher in the HT and HFPEF groups than in the Normal group. These indices did not differ between the HT and HFPEF groups. Left atrial dimension, tricuspid regurgitation peak gradient and E/E' ratio were the highest in the HFPEF group and the lowest in the Normal group.

S' was significantly lower in the HFPEF and HT groups

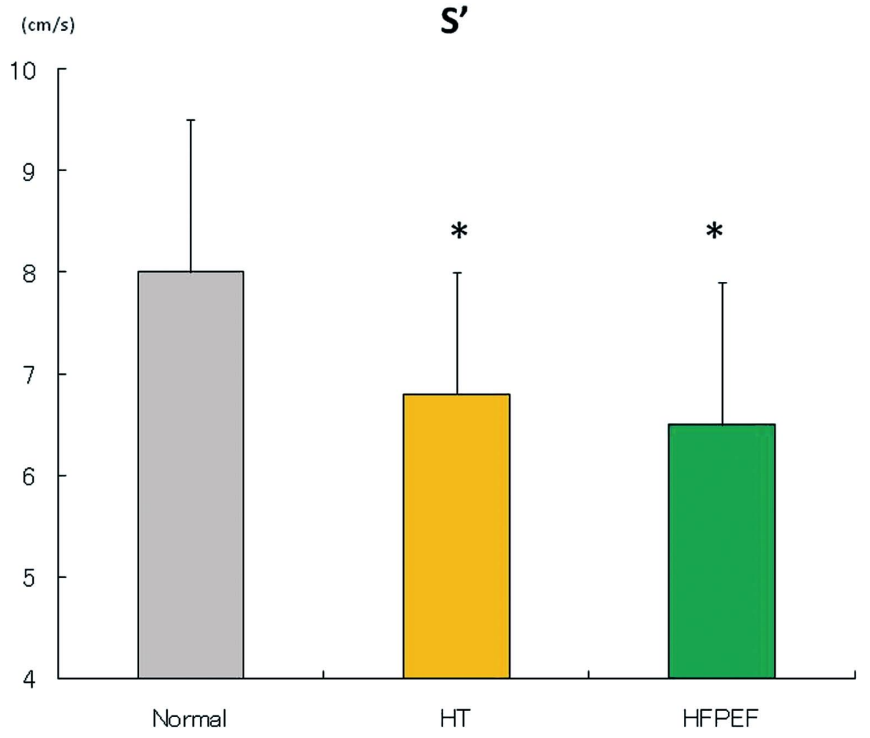

Figure 1. Comparison of S' among the Normal, HT and HFPEF groups. *P<0.05 vs. Normal group. S', peak systolic myocardial velocity at septal position recorded by tissue Doppler imaging. HFPEF, heart failure with preserved ejection fraction; HT, hypertension.

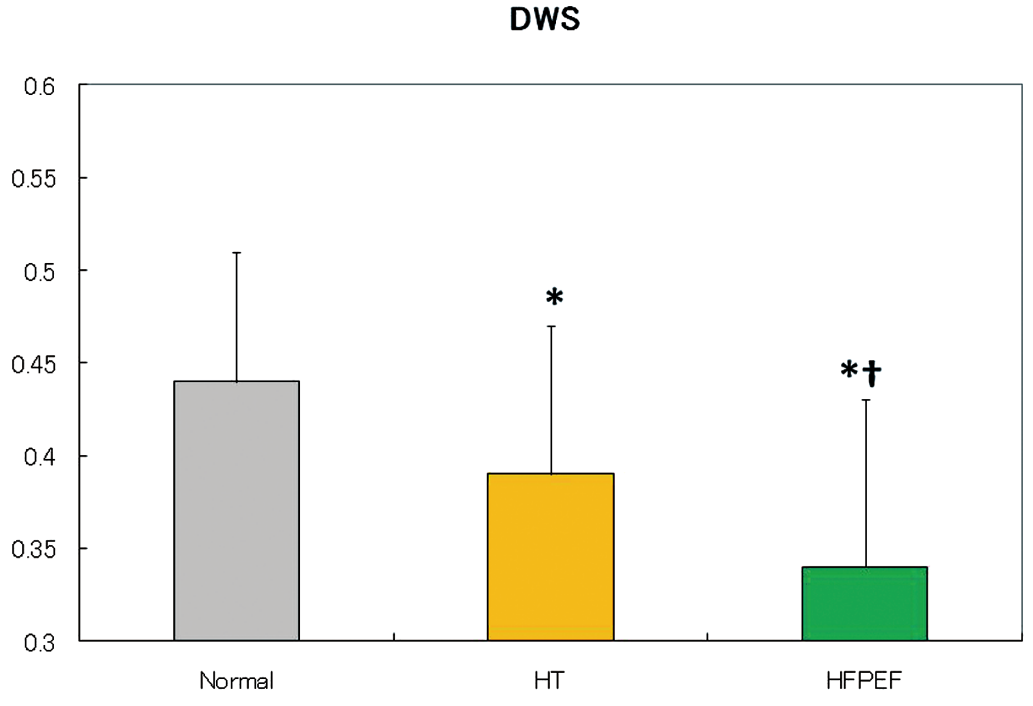

Figure 2. Comparison of diastolic wall strain (DWS) among the Normal, HT and HFPEF groups. *P<0.05 vs. Normal group. †P<0.05 vs. HT group. HFPEF, heart failure with preserved ejection fraction; HT, hypertension.

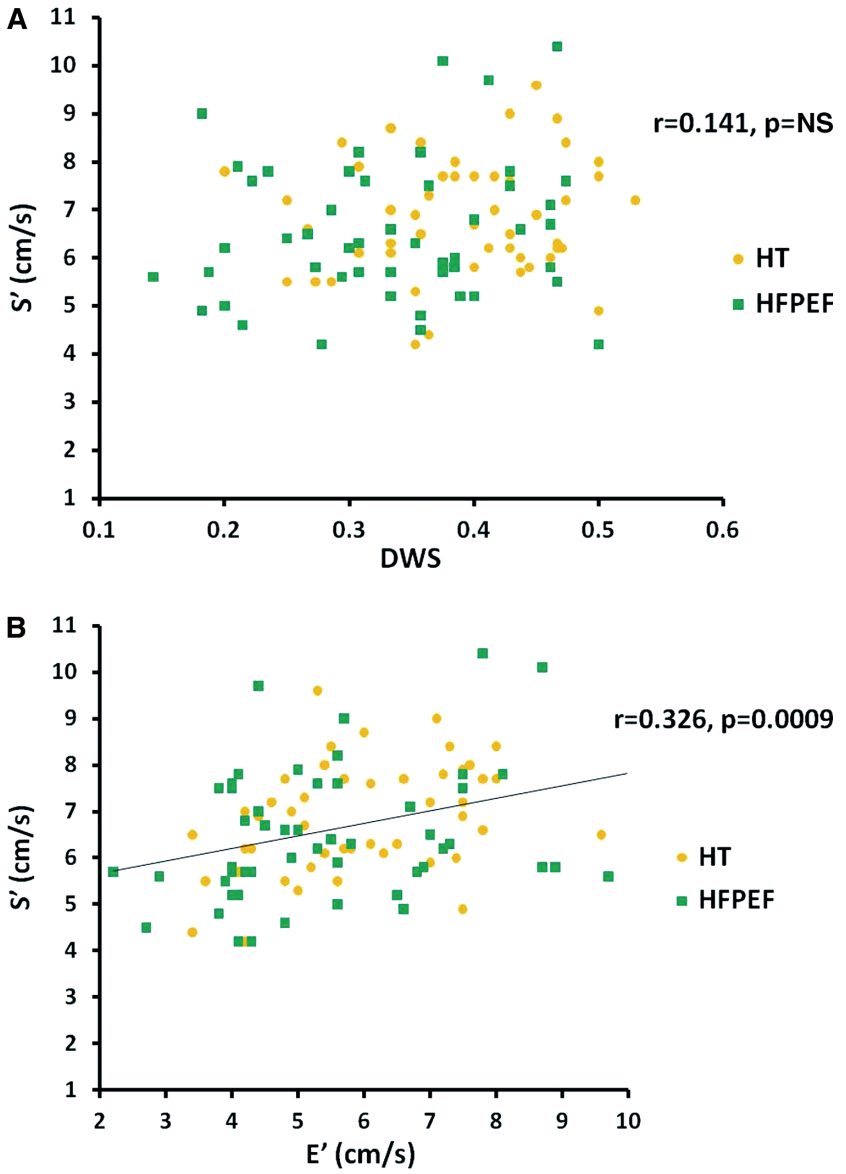

Figure 3. (**A**) Correlation between S' and DWS in patients of HFPEF and HT groups. (**B**) Correlation between S' and E' in patients of HFPEF and HT groups. E', peak early diastolic myocardial velocity at septal position recorded by tissue Doppler imaging; HFPEF, heart failure with preserved ejection fraction; HT, hypertension; S', peak systolic myocardial velocity at septal position recorded by tissue Doppler imaging.

than in the Normal group, and was not significantly different between the HT and HEPEF groups (**Figure 1**). DWS was lowest in the HFPEF group and highest in the Normal group (**Figure 2**). There was no significant correlation between S' and DWS in the patients of the HFPEF and HT groups (**Figure 3A**). In contrast, S' significantly correlated with E' (**Figure 3B**).

The same analysis was conducted only in patients without elevated LV filling pressures (ie, patients with E/E' ratio <15).[22] DWS was significantly lower in the HFPEF group (n=43) than in the HT group (n=48) (0.33±0.09 vs. 0.39±0.07, P<0.05). S' did not differ between the 2 groups.

Discussion

The results of the current study showed that LV longitudinal systolic function and LV relaxation were impaired to the same degree in the HT and HFPEF groups, but that LV distensibility, as assessed by DWS, was further exacerbated in the HFPEF group compared to the HT group.

Our animal experimental study showed that the impairment of LV compliance/distensibility progresses, but LV relaxation abnormality does not, in the transition from asymptomatic LV diastolic dysfunction to the HFPEF stage in a hypertensive HFPEF model.[11] The currently available noninvasive indices for LV diastolic function represent LV relaxation (E' or flow propagation velocity of early diastolic flow)[12,23] or LV filling pressure (E/E'),[22] and it has been difficult to noninvasively assess LV compliance or distensibility. We recently demonstrated that DWS inversely correlates with the myocardial stiffness constant and is not affected by preload alteration.[13] The current study showed that DWS was lower in HFPEF patients than in asymptomatic hypertensive patients, despite similar decreases in S' and E'. The same results were obtained even when excluding patients with elevated LV filling pressure. Thus, the significant difference in DWS between the HFPEF and HT groups cannot be explained by the high prevalence of patients with an elevated

LV filling pressure in the HFPEF group compared to the HT group, and progressive exacerbation of LV distensibility may play a crucial role in the development of HFPEF. Melenovsky et al reported that LV hypertrophy and left atrial dilatation, not low S', were cardiovascular features that discriminated patients with HFPEF from those with asymptomatic LV hypertrophy.[24] In this study, the left atrial dimension was greater in the HFPEF group than in the HT group, but the LV mass index was not different between the 2 groups. Left atrial enlargement indicates LV diastolic dysfunction,[25] but also reflects abnormality of both LV relaxation and distensibility. Vinereanu et al showed a significant correlation of S' with the indices of LV relaxation and filling pressure, and concluded that diastolic function was impaired in parallel with systolic function.[26] The significant correlation between the indices for systolic function and relaxation was also observed in our study, as indicated by the correlation between S' and E' (**Figure 3B**). Vinereanu et al did not assess LV distensibility, and we demonstrated a lack of correlation between S' and DWS (**Figure 3A**). The results of the present study suggest that the development of HFPEF from the asymptomatic stage is associated with progressive LV diastolic dysfunction, which is primarily due to exacerbation of LV distensibility. In addition, we demonstrated that diastolic function is not impaired in parallel with systolic function if LV distensibility is evaluated in the assessment of diastolic function. Our recent preliminary study demonstrated that HFPEF patients with low DWS have a poor prognosis.[27] Thus, LV distensibility is likely to play a crucial role in the pathogenesis of this type of HF.

Several previous studies have reported that S', the most sensitive marker of systolic function,[19–21] was reduced in patients with HFPEF,[5–8] and have argued that HFPEF is caused by systolic dysfunction. However, those previous studies compared HFPEF patients to normal subjects. Redfield et al showed that there are many asymptomatic patients with diastolic dysfunction,[9] indicating that there is a stage of asymptomatic diastolic dysfunction between the normal and HFPEF stages. We found that the S' of HFPEF patients was decreased as compared to normal subjects, which is compatible with the findings of previous studies;[5–8] however, we also demonstrated that S' did not differ between asymptomatic hypertensive patients and HFPEF patients. These observations are partly supported by the data from other studies.[24,26] Thus, the progression of systolic dysfunction may not be the principal cause for the transition from asymptomatic diastolic dysfunction to HFPEF. Yu et al reported that S' was lower in patients with HFPEF than in those with asymptomatic diastolic dysfunction, and suggested the contribution of progressive systolic dysfunction to HFPEF.[28] However, E' was also significantly lower in patients with HFPEF than in those with asymptomatic diastolic dysfunction, and LV distensibility was not assessed in their study. In our study, E' was similarly decreased in the HFPEF and HT groups (**Table 2**). Thus, the diastolic function of patients with asymptomatic diastolic dysfunction may have been impaired to a lesser degree in Yu's study than in our study, which would explain the different conclusions.

Study Limitations

First, this hospital-based study provided cross-sectional observations only and cannot adequately prove causality. Second, it was a retrospective study, and medications were not withheld for echocardiographic examination of patients of the HT and HFPEF groups. Third, the number of study subjects was not large. Fourth, brain natriuretic peptide levels were not measured, and it is unclear how many patients met the criteria of HFPEF proposed by the European Society of Cardiology.[29] Fifth, all the study subjects were Japanese. A number of demographic parameters may affect the cardiovascular abnormalities and comorbidities in HFPEF patients, and the current results may not be able to be simply extrapolated to other races. Sixth, the Normal group was not matched by age with the HT and HFPEF groups. The difference in some parameters between the Normal and HT groups may be partly explained by aging rather than hypertension. However, there was no difference in age between the HT and HFPEF groups, and our conclusion about the factors that are related to the transition from the asymptomatic stage with diastolic dysfunction to the HFPEF stage may not be affected by the difference in age between the Normal group and the HT or HFPEF group.

Conclusions

The current study results suggest that the transition from the asymptomatic stage with diastolic dysfunction to the HFPEF stage can not be attributed to progression of systolic abnormality, and that exacerbation of LV distensibility plays a crucial role in the development of HFPEF.

Acknowledgments

The authors are grateful to Ms Keiko Katsuki and Ms Yumiko Kobayashi for their technical assistance. Shunsuke Tamaki, MD is a research assistance of the Global COE Program.

Disclosures

Conflict of Interest: None declared.

Funding Sources: This study was supported in part by grants from the Japanese Society for the Promotion of Science.

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