Evidence of Left Ventricular Systolic Dysfunction Detected by Automated Function Imaging in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction

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ABSTRACT

Background: Left ventricular ejection fraction (LVEF) cannot reflect cardiac contractile function in patients with heart failure and preserved LVEF (HFPEF). LV systolic impairment is actually debated in HFPEF patients. Automated function imaging (AFI) is a novel algorithm of speckle-tracking echocardiography and efficiently to assess global LV peak systolic longitudinal strain (PSLS), an index for systolic function. The purpose of the study is to examine whether contractile function is impaired in HFPEF patients.

Methods and Results: This study included 49 heart failure patients (23 with systolic dysfunction [SHF] and 26 with HFPEF), and 40 patients, matched for age, sex, as well as concomitant disease and without heart failure as controls. All patients underwent transthoracic echocardiography. LVEF was measured by Simpson's method. Two-dimensional speckle tracking imaging with AFI assessment was applied to measure longitudinal strain. LVEF was 66 ± 5% in the controls, 63 ± 8% in the HFPEF group ($P = .14$), and 34 ± 10% in the SHF group ($P < .001$). The value of LV global PSLS (controls: −20%, HFPEF: −14%, SHF: −8%, $P < .001$) was significantly less negative in both heart failure groups.

Conclusions: Deteriorated LV systolic function is demonstrated by decreased global PSLS in HFPEF patients. AFI is an effective and facile method for assessing LV systolic abnormalities. (*J Cardiac Fail 2009;15:782−789*)

Key Words: Heart failure with preserved left ventricular ejection fraction, automated function imaging, peak systolic longitudinal strain.

To evaluate left ventricular global systolic function, several echocardiographic techniques are available, including a modified Simpson method, formulae for calculating left ventricular ejection fraction (LVEF) from 2-dimensional volumes or 2-dimensional directed M mode, or fractional shortening. The assessment of LVEF is essential for definite diagnosis, further prognosis, and adaptable therapy. More than 50% of patients who present with heart failure symptoms have preserved LV systolic function.[1] This patient group has been diagnosed as diastolic heart failure or heart failure with preserved LV ejection fraction (HFPEF),[2−4] whose mortality rate is similar to that of patients with systolic heart failure (SHF).[2]

Global LVEF reflects the sum of all regional shortening in the left ventricle, but is normalized for end-diastolic volume that is equally important, in particular in heart failure with dilated hearts. Regional wall motion impairment may not reduce LVEF unless several segments are involved. As a result, methods that can measure left ventricular regional function or myocardial contractility can be more sensitive than global EF for identifying systolic dysfunction in heart failure patients. Many reports[5−9] suggested that using tissue Doppler imaging, depressed myocardial contractility presenting with reduced peak systolic myocardial velocity was evident in HFPEF patients; meanwhile, other studies

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did not confirm this finding.[10–12] Therefore, LV systolic dysfunction detected in the HFPEF patients remains in doubt.

Notwithstanding, speckle tracking echocardiography measures the myocardial deformation (strain) and is superior to myocardial velocities in assessment of LV systolic performance because of the ability to detect myocardial deformation and slight alternations in systolic function.[13] We hypothesized that alterations of myocardial contractility could be detected in patients with HFPEF by using speckle tracking echocardiography, processed by a more sensitive and semiautomated measured algorithm, automated function imaging (AFI). Thus, this study aimed at detecting whether there is systolic dysfunction in HFPEF patients and at elucidating the probable mechanisms.

Methods

Study Subjects

Fifty-two consecutive patients presenting with congestive heart failure (age: 66 ± 16 years) were enrolled in the National Cheng University Hospital Dou-Liou Branch, a community hospital in mid-Taiwan. They suffered from dyspnea, orthopnea, and paroxysmal nocturnal dyspnea; pulmonary edema was found by chest X-ray. Heart failure status was ascertained by the New York Heart Association classification of functional status[14] and Framingham criteria for the diagnosis of congestive heart failure.[15] Patients were classified as having SHF or HFPEF according to LVEF and LV end-diastolic volume index (LVEDVI).[2] Patients with LVEF <50% were classified as having SHF and those with LVEF ≥50% and LVEDVI <97 mL/m^2 were classified as having HFPEF. Forty-one patients (age 67 ± 7 years) were included as controls. They received echocardiographic examination because of dyspnea or the underlying concomitant diseases (ie, hypertension, diabetes mellitus, coronary artery disease), and did not have symptoms of heart failure. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of National Cheng Kung University Hospital.

Echocardiographic Measurements

All of the patients were examined in the left lateral decubitus position, using a commercially available ultrasound system with a 3.5 MHz probe (Vivid-7, GE Healthcare, Horten, Norway). Quantification of LV mass, volume, and EF were performed according to the recommendations of the American Society of Echocardiography.[16] Pulse-waved Doppler examination was performed for mitral inflow measurements included peak early flow velocity (E) and the deceleration time of early mitral flow velocity. The sample volume was placed at the tip of the mitral valve and oriented parallel to the blood flow direction. Two-dimensional grayscale images were acquired in the standard 3 apical views (apical 4-chamber, apical 2-chamber, and apical long-axis) at a frame rate of 40 to 90 frames/s, and 3 cardiac cycles were recorded.[17] Pulsed tissue Doppler imaging (TDI) of the mitral annulus movement was acquired from the apical 4-chamber view when a 1.5-mm sample volume was placed sequentially at the septal and lateral mitral annular sites.[18] We measured the systolic (S′) and early (E′) diastolic peak velocities at septal and lateral annular sites.[19–21] The E/E′ ratio was calculated from the average of the septal and lateral E′. All images were stored digitally for subsequent offline analysis.

Echocardiographic Analysis

Two cardiologists performed offline analysis by using commercial software, AFI (EchoPAC work station, BT06, GE Healthcare, Israel) without knowledge of the clinical information. The tracking algorithm follows the endocardium from this single frame throughout the cardiac cycle and allows for a further manual adjustment of the region of interest to ensure that the whole layers of myocardium, from endocardium to epicardium, are included. The subendocardial fibers and the trabecular endocardial myocardium are not involved. Values of the peak systolic longitudinal strain (PSLS) from the apical long-axis, apical 4-chamber, and apical 2-chamber views were obtained automatically by AFI software (Fig. 1). The average of the 3 values was regarded as global LV peak systolic longitudinal strain (GPSLS_Avg).

Statistical Analysis

SPSS software (version 15.0, SPSS Inc, Chicago, IL) was used for statistical analysis. Continuous data are presented as mean ± standard deviation (SD) and dichotomous data are presented as a number and percentage. Comparisons were carried out with 1-way analysis of variance. Multiple comparison procedures were performed using the Scheffe method. The relationship between continuous variables was analyzed using regression analysis. Receiver-operating characteristics analysis was used to select cutoff values to distinguish HFPEF patients from normal controls. The intra- and inter-rater reliability were assessed for the measurement of GPSLS_Avg in 2 sets of 10 randomly selected subjects using Bland-Altman limits of agreement[22] and Interclass correlation coefficient. Two-sided P value ≤.05 was considered statistically significant.

Results

Clinical Characteristics

There were 93 patients included in the study: 27 with HFPEF, 25 with SHF, and 41 without heart failure as controls. All patients underwent echocardiography. However, because of inadequate images for reliable AFI analysis, 4 subjects (1 in the control group, 2 in the SHF group, and 1 in the HFPEF group) were excluded. Patient characteristics and concomitant diseases are presented in Table 1. No difference existed between groups with respect to age, gender, and concomitant diseases. In the HFPEF group, 80% patients had at least New York Heart Association Class Functional Class III.

Cardiac Function

All investigated patients of the HFPEF and control groups showed normal LVEDVI, less than 97 mL/m^2. LVEDVI, LV end-systolic volume, deceleration time, the TDI systolic mitral annular velocity (S′), E′, E/E′, and LVEF were significantly different in the SHF group compared with the HFPEF and control groups ($P < .05$, Table 2). However, these variables, except S′, were not significantly different between the HFPEF and control groups ($P > .05$). Furthermore, LV mass and left atrial dimension were significantly higher in the SHF and HFPEF groups ($P < .01$).

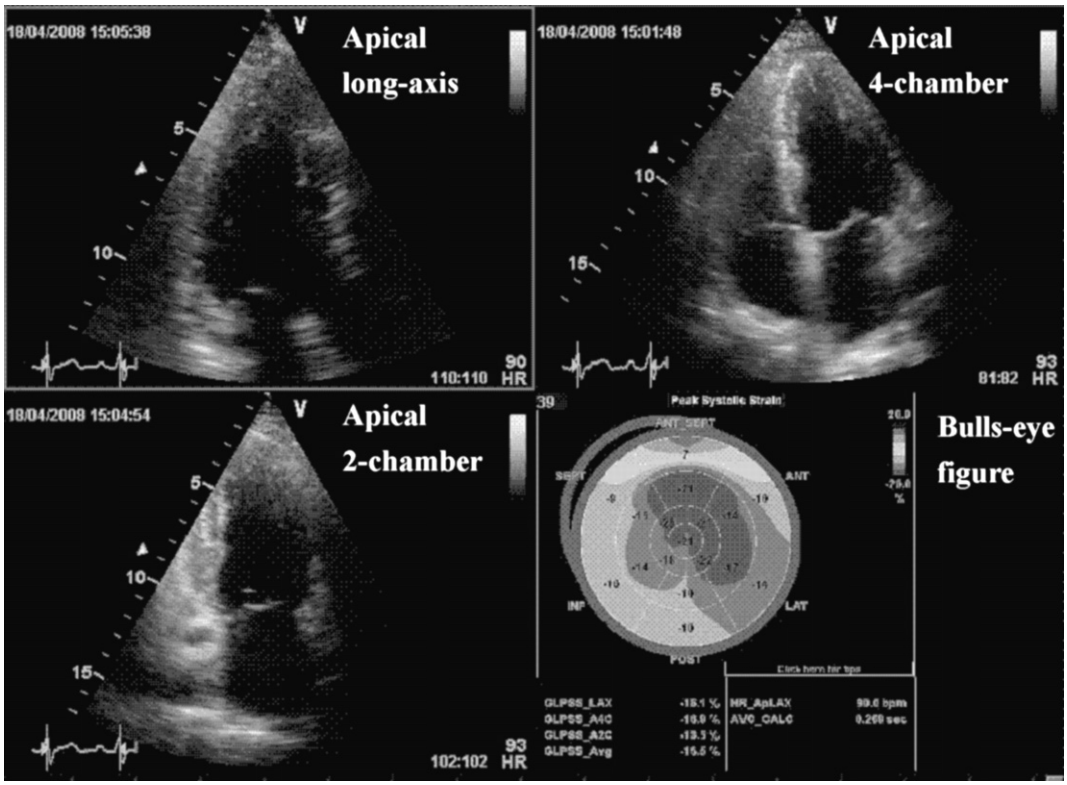

Fig. 1. Example of global left ventricular peak systolic longitudinal strain graph. Values of the peak systolic longitudinal strain (PSLS) from the apical long-axis, apical 4-chamber (A4C), and apical 2-chamber (A2C) views were obtained automatically by AFI software. The average of the 3 values was regarded as global left ventricular peak systolic longitudinal strain (GPSLS_Avg).

In patients with HFPEF, the ratio E/E′ was 15.9 ± 7.2, compatible with diagnostic evidence of presence of diastolic LV dysfunction in HFPEF.[2] Compared with the controls, patients with HFPEF tended to have a higher E/E′, but the difference did not reach statistical significance (Table 2).

The GPSLS_Avg was significantly less negative in the HFPEF group than in the control group ($P < .001$). Subsequently, we analyzed the values of the apical long-axis, 4-chamber, and 2-chamber views, and the segmental values of peak systolic longitudinal strain. Marwick and his colleagues[23] recently reported segmental normal range of LV longitudinal strain: −13.7 to −20.1% at basal-LV, −16.8 to −20.4% at mid-LV, and −17.7 to −22.5% at apical-LV. Comparing with the reference values,[23] it will be regarded as abnormal in our study if the value of segmental strain is less than the reference values. It was found that all the enrolled patients had a decreased value of peak systolic longitudinal strain in at least one segment, especially in the basal anteroseptal segment (Table 3).

Differentiation of HFPEF Patients from the Controls

LVEF was not significantly different between the HFPEF patients and the controls; most important of all, the GPSLS_Avg was significantly more negative in the controls than the HFPEF patients (controls −19.7 ± 2.4% vs. HFPEF patients −14.0 ± 4.5%, $P < .001$, Fig. 2A, 2B). The Scatter diagram showed the correlation coefficient of

Table 1. Clinical characteristics of the study subjects

Variables	HFPEF (n = 26)	SHF (n = 23)	Control (n = 40)	*P* Value*
Age (years)	68 ± 13	63 ± 18	67 ± 7	.718
Female gender, n (%)	8 (31)	10 (43)	19 (48)	.439
BMI, kg/m^2	27.4 ± 5.5	25.5 ± 4.5	26.4 ± 3.8	.380
CAD, n (%)	7 (27)	18 (78)	17 (43)	.793
Diabetes mellitus, n (%)	10 (38)	8 (35)	13 (33)	.436
Hypertension, n (%)	23 (88)	17 (74)	29 (72)	.214
SBP, mm Hg	142 ± 20	141 ± 23	137 ± 26	.297
DBP, mm Hg	83 ± 17	80 ± 18	75 ± 18	.084

BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HFPEF, heart failure with preserved left ventricular ejection fraction; SBP, systolic blood pressure; SHF, systolic heart failure.

Data are expressed as mean ± SD, or number (%).

*P value in this column was from the comparison between HFPEF group and control group.

Table 2. Echocardiographic measurements

Variables	HFPEF (n = 26)	SHF (n = 23)	Control (n = 40)	*P* Value*
LVEDV, mL	132 ± 58	182 ± 52†	117 ± 27	.136
LVESV, mL	51 ± 30	117 ± 50†	40 ± 10	.222
LVEVDI, mL/m^2	77.1 ± 19.1	113.1 ± 26.2†	70.1 ± 15.6	.310
LA parasternal, mm	39.9 ± 7.7	41.0 ± 7.0†	35.2 ± 4.8	.008
LVEF, %	63.2 ± 8.1	34 ± 10†	65.9 ± 5.4	.140
LV mass, g	247 ± 120	259 ± 128†	175 ± 46	.006
DT, ms	184 ± 70	147 ± 78†	200 ± 53	.241
E′, m/s	0.06 ± 0.02	0.04 ± 0.02†	0.06 ± 0.02	.666
S′, m/s	0.07 ± 0.03	0.05 ± 0.02†	0.09 ± 0.02	<.001
E/E’	15.9 ± 7.2	25.0 ± 14.0†	12.6 ± 3.5	.152
GPSLS_Avg, %	−14.0 ± 4.5	−8.1 ± 3.4	−19.7 ± 2.4	<.001

DT, deceleration time; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EF, ejection fraction; ESV, end-systolic volume; GPSLS_Avg, average of global peak LV longitudinal strain; LA, left atrium; LV indicates left ventricular.

Data are expressed as mean ± SD.

**P* values in this column were from the comparison between HFPEF group and control group.

†*P* < .05 was from the comparison between the SHF group and the HFPEF or control group.

−0.40 and 0.07 between LVEF and GPSLS_Avg in HFPEF patients and controls, respectively (Fig. 2C, 2D). The best cutoff value obtained by means of receiver-operating characteristics curve analysis for GPSLS_ Avg was −17.5% at a sensitivity of 85% and specificity of 85% with an area under the curve of 0.88 (Fig. 3).

Inter- and Intra-rater Variability

There was excellent intra-rater and inter-rater agreement by using AFI to calculate GPSLS_Avg. The intra-rater and inter-rater interclass correlation coefficients of the average measures were 0.995 (95% confidence interval [CI]: 0.986-0.998) and 0.986 (95% CI: 0.949-0.996), respectively. The mean intra-rater and inter-rater differences (mean ± SD) were −0.41 ± 0.87 (−2.12 to 1.31) and −0.13 ± 1.20 (−2.48 to 2.22), respectively (Fig. 4).

Discussion

Our study showed that LV systolic dysfunction, represented as decreased LV global peak systolic longitudinal strain, can be observed in patients with so-called HFPEF. Decreased global LV PSLS was probably the result of regional decline of LV longitudinal strain in HFPEF patients, and it could not be reflected by LVEF measurement. Using LV global longitudinal strain, HFPEF patients can be distinguished from controls. Briefly, AFI is an efficient and accurate assessment to approach the value of LV global PSLS, which has a higher diagnostic value than echocardiographic indexes, such as LVEF, and E/E′ ratio, for the evaluation of HFPEF and the detection of differences between the HFPEF patients and the controls.[12,24] To our knowledge, our study is the first to investigate the application of AFI in HFPEF patients, and most importantly, to clarify systolic dysfunction in HFPEF patients.

Table 3. Abnormal segmental peak systolic longitudinal strain in 26 heart failure patients with preserved left ventricular ejection fraction, n (%)

	Anterior	Anteroseptal	Septal	Inferior	Posterior	Lateral
Basal	25 (96)	26 (100)	24 (92)	15 (58)	15 (58)	23 (89)
Mid	22 (85)	17 (65)	21 (81)	17 (65)	19 (73)	23 (89)
Apical	12 (46)	14 (54)	19 (73)	18 (69)	13 (50)	16 (62)

Diagnosis of Heart Failure with Preserved LVEF

Diagnosis of HFPEF is a challenge for physicians because there is a lack of consensus on specific criteria and the absence of noninvasive tests to confirm the diagnosis.[25] Clinical symptoms and signs are nonspecific and cannot differentiate HFPEF from SHF.[26] The European Society of Cardiology proposed that all of the following conditions had to be satisfied for the diagnosis of HFPEF[2]: 1) presence of signs or symptoms of congestive heart failure; 2) presence of normal or mildly abnormal LV systolic function as LVEF > 50% and left ventricular end-diastolic volume index < 97 mL/m^2; and 3) evidence of diastolic LV dysfunction.

Because of the characteristics of noninvasiveness, echocardiography plays an important role in diagnosing diastolic LV dysfunction in HFPEF patients. There are several echocardiographic parameters, such as mitral inflow Doppler pattern, pulmonary venous inflow Doppler, and tissue Doppler, that can be used to help in the diagnosis of diastolic dysfunction; however, none is diagnostic.[2,27,28] Actually, it is recommended that the presence of multiple abnormalities is strongly suggestive of diastolic dysfunction.[25]

TDI has been proved to be more accurate than conventional echocardiographic modalities for detecting impaired diastolic function in HFPEF patients.[17,27] It is recommended by the European Society of Cardiology that E/E′ > 15 is diagnostic evidence of LV diastolic dysfunction.[2] In our study, HFPEF patients had the same result by using TDI measurement. In the ratio E/E′, effects of LV relaxation kinetics and age are considered to be eliminated and the ratio is a measure of LV filling pressure.[29,30] However, Sutter and colleagues demonstrated that age was the most important determinant of E/E′, and mean E/E′ of old patients (age of 65−74 years) with hypertension was 12.6.[31] In our study, we had the similar result, and the

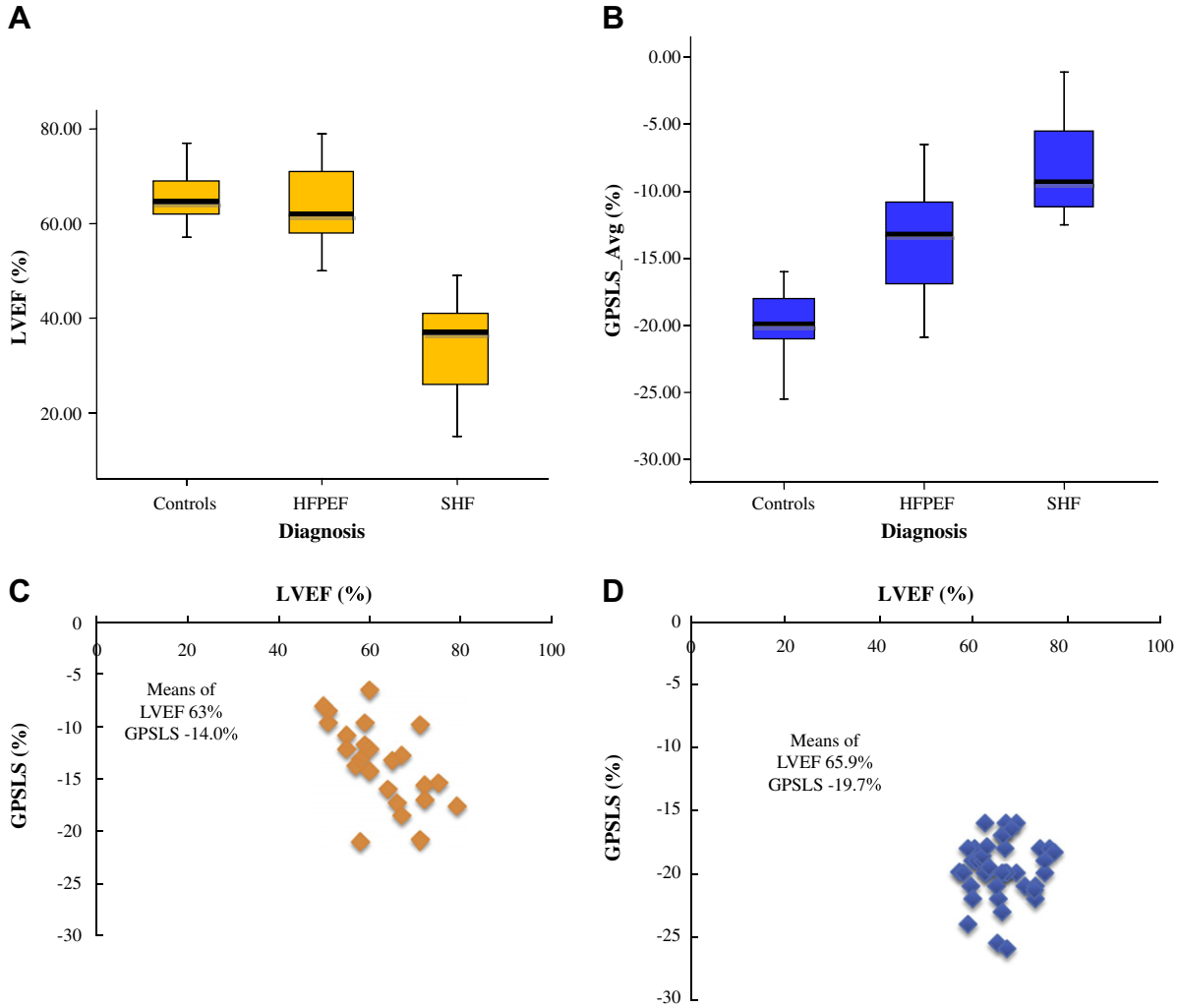

Fig. 2. Comparisons between groups with regard to left ventricular ejection fraction (LVEF, A) and global LV peak systolic longitudinal strain (GPSLS_Avg, B). Scatter diagram showing the relationship between LVEF and GPSLS_Avg of HFPEF (C) and controls (D) with correlation coefficient of −0.40 and 0.07 respectively. LVEF and GPSLS_Avg were significantly lower in the systolic heart failure (SHF) patients compared with the controls. In the heart failure patients with preserved LVEF (HFPEF), LVEF was not significantly different compared with the controls; however, GPSLS_Avg was significantly lower.

difference between the controls and the HFPEF patients did not reach statistical significance. And most important of all, LV GPSLS_Avg had a higher accuracy than TDI parameters for diagnosis of HFPEF.

Assessment of LV Function by Speckle-tracking Echocardiography

Angle-dependency is the major limitation of all Doppler-based techniques. Speckle-tracking echocardiography has been introduced as a method for angle-independent quantification of myocardial strain.[28] Speckles are natural acoustic markers, seen as small and bright elements in conventional grayscale ultrasound images, and distributed equally in the myocardium.[32] The distance between selected speckles is a direct measure of myocardial deformation.[13] It is strongly suggested that strain measurements based on speckle tracking are able to detect small alterations in systolic function.[32,33] AFI is a novel algorithm of speckle tracking which can be easily performed and is time saving and more reproducible for measurement of PSLS.

Detection of LV Systolic Dysfunction in HFPEF

It is controversial whether impaired systolic function can be detected in HFPEF patients. Several studies[5–9] have found reduced global or regional systolic peak velocities in patients with HFPEF. Yip and colleagues[7] demonstrated that in patients with HFPEF and evidence of LV hypertrophy, there was systolic LV impairment as measured by mitral annular peak velocity and amplitude by TDI. Wang et al[9] found that the LV longitudinal and radial strains, not circumferential strain and torsion, are reduced in HFPEF patients. Although the difference of longitudinal strain between the HFPEF group and the normal healthy control group is significant, yet the controls are much younger than the HFPEF patients and do not have any underlying diseases (eg, coronary artery diseases, diabetes mellitus,

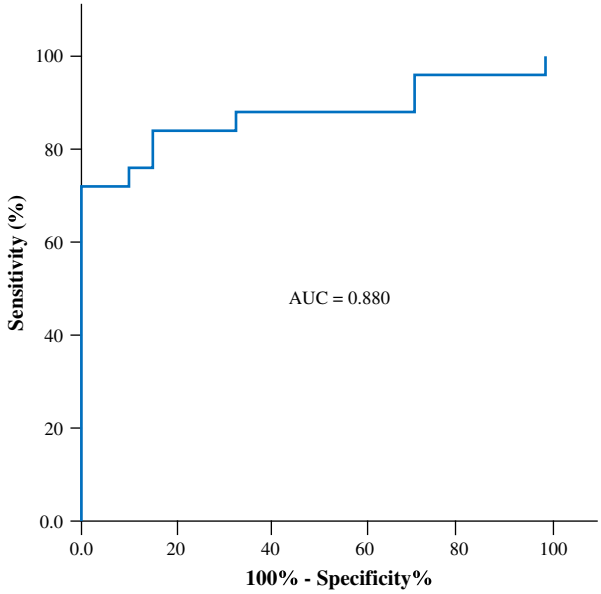

Fig. 3. Receiver operating characteristics curve analysis for the accuracy of global left ventricular (LV) longitudinal strain in differentiating patients with heart failure and preserved LV ejection fraction from controls. AUC, area under the curve.

hypertensive cardiovascular disease), which may result in reduction of longitudinal myocardial deformation.[34] Therefore, it could not be ascertained that the reduced longitudinal strain is resulted from heart failure, aging, or other concomitant disease.

In this study, we measured LV longitudinal strain by speckle-tracking echocardiography and calculated global and regional PSLS by using AFI in HFPEF patients and the age- and gender-matched control group. Interestingly, LVEF was not different between the HFPEF patients and the controls, but comparing these 2 groups, a significantly higher global PSLS value was detected in the former (Fig. 2). Based on "single syndrome" hypothesis of heart failure,[35,36] HFPEF and SHF are assumed to be extreme phenotypes in the spectrum. Thus, patients with HFPEF present with regional disturbances in long-axis function and diastolic dyssynchrony.[37]

Reasons for LV Systolic Deterioration in HFPEF

HFPEF patients are usually old, and have many concomitant diseases, such as hypertension, diabetes mellitus, or coronary artery diseases. These diseases can result in LV macrovascular or microvascular abnormalities as well as interstitial fibrosis. Because the endocardium is most sensitive to deleterious effects of hypoperfusion or ischemia, the deteriorated LV longitudinal function can be detected at an earlier stage by measuring strain.[9,38] In addition, all HFPEF patients had reduced PSLS of LV regional wall. The results indicated that deterioration in LV systolic function can be detected by AFI in HFPEF patients with or without preexisting coronary artery diseases. Moreover, our findings also reflect the subendocardial position of the

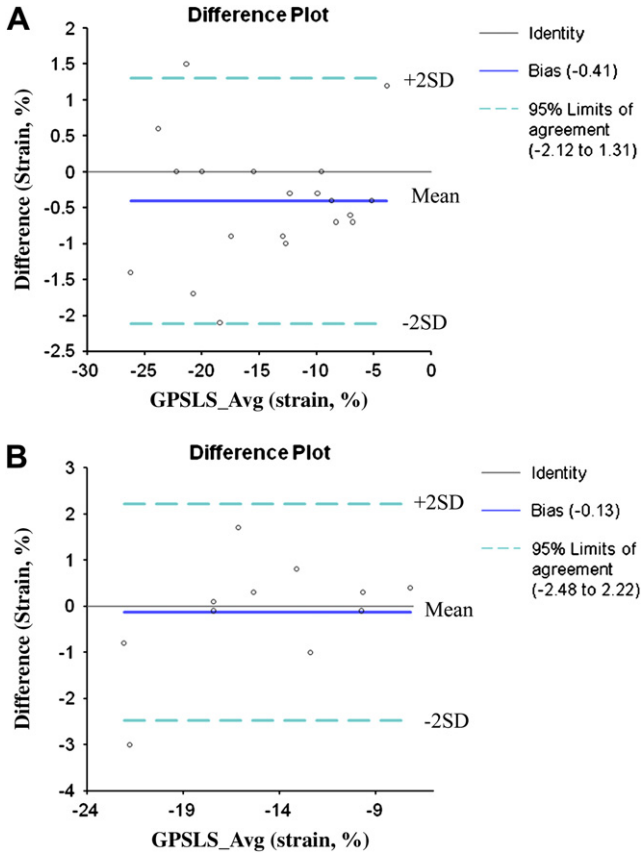

Fig. 4. Bland and Altman analysis of global left ventricular peak systolic longitudinal strain (GPSLS_Avg) of (A) intraobserver and (B) interobserver variability.

longitudinal fibers making them more vulnerable to ischemia, ventricular hypertrophy, and any abnormalities of activation and relaxation.[39,40] In the present study, we measured global LV longitudinal strain of the whole myocardium by the novel algorithm AFI, and the region of interest was not limited to any specific layer of myocardium, such as epicardial or endocardial myofibers.[23,41] Therefore, although ischemia and hypoperfusion of the subendocardium may play a role, we have yet to recognize that other mechanisms should be involved. The actual mechanism is deserved further investigation.

Limitations

The findings of the current study rely on noninvasive methods. We recognize that invasive measurements of the ventricular pressure-volume relationship are still the gold standard for diagnosing HFPEF. However, invasive measurements can just only be applied to a very small number of patients. Therefore, a noninvasive approach is still required for assessing patients with suspicion of HFPEF. The heart failure biomarker, brain natriuretic peptide, is recommended for exclusion of HFPEF,[2] but not available in our hospital. However, echocardiography can tell us more information of HFPEF patients than brain natriuretic peptide does. Moreover, our study is limited by medium amount of number

of patients. Besides, 1 limitation of the present study is lack of a healthy age- and sex-matched control group. Because the HFPEF patients are usually much older, it is difficult to include the healthy senior citizen as controls. To overcome this limitation, we included age- and gender-matched patients without obvious structural heart diseases by echocardiography as the control group. Furthermore, concomitant disease and risk factors were distributed equally among groups to avoid the influences of these factors. Although the difference between the HFPEF patients and the controls was quite significant, these data should be confirmed in a large number of subjects.

Conclusions

LV global PSLS is reduced in HFPEF patients in comparison with controls. Decline of systolic function can be demonstrated by decreased global PSLS in patients with HFPEF. AFI is a novel, angle-independent, more reproducible, and apparently simpler and computationally faster speckle tracking technique. It is easy to use for assessment of LV systolic abnormalities.

References

1. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557−62.
2. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademalers FE, et al. How to diagnose diastolic heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539−50.
3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317−27.
4. Sanderson JE. Heart failure with a normal ejection fraction. Heart 2007;93:155−8.
5. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with ''isolated'' diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195−201.
6. Petrie MC, Caruana L, Berry C, McMurray JJ. ''Diastolic heart failure'' or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002;87:29−31.
7. Yip G, Wang M, Zhang Y, Fang JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121−5.
8. Vinereanu D, Nicolaides E, Tweddel AC, Fraser AG. ''Pure'' diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. Eur J Heart Fail 2005;7:820−8.
9. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283−9.
10. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953−9.
11. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296−304.
12. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation 2007;116:637−47.
13. Edvardsen T, Helle-Valle T, Smiseth OA. Systolic dysfunction in heart failure with normal *ejection* fraction: speckle-tracking echocardiography. Prog Cardiovasc Dis 2006;49:207−14.
14. Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of the heart and great vessels. 9th ed. Boston: Little, Brown; 1994.
15. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441−6.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. Developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440−63.
17. Notomi Y, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004;17:630−3.
18. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527−33.
19. Quinones MA. Assessment of diastolic function. Prog Cardiovasc Dis 2005;47:340−55.
20. Urheim S, Edvardsen T, Torp H. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 2000;102:1158−64.
21. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressure. J Am Coll Cardiol 1997;30:1527−33.
22. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307−10.
23. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range. JACC Cardiovasc Imaging 2009;2:80−4.
24. Hill JC, Palma RA. Doppler tissue imaging for the assessment of left ventricular diastolic function: A systemic approach for the sonographer. J Am Soc Echocardiogr 2005;18:80−90.
25. Shammas RL, Khan NUA, Kekkanti R, Movahed A. Diastolic heart failure and left ventricular diastolic dysfunction: what we know, and what we don't know! Int J Cardiol 2007;115:284−92.
26. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I. Circulation 2002;105:1387−93.
27. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnosis of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 2005;26:2277−84.
28. Bohs LN, Trahey GE. A novel method for angle independent ultrasonic imaging of blood flow and tissue motion. IEEE Trans Biomed Eng 1991;38:280−6.
29. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788−94.
30. Dokainish H, Zoghbi WA, Lakkis NM, AL-Bakshy F, Dhir M, Quinones MA, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 2004;109:2432−9.
31. Sutter JD, Backer JD, Veire NV, Velghe A, Buyzere MD, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral

annulus velocity (E′) and the ratio of transmitral early peak velocity of E′ (E/E′). Am J Cardiol 2005;95:1020−3.
32. Leitman M, Lysyansky P, Sidenko S. Two-dimensional strain—a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004;17:1021−9.
33. Suffoletto MS, Dohi K, Cannesson M. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960−8.
34. Bijnens BH, Cikes M, Claus P, Sutherland GR. Velocity and deformation imaging for the assessment of myocardial dysfunction. Eur J Echocardiogr 2009;10:216−26.
35. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure: different phenotypes of the same disease? Eur J Heart Fail 2007;9: 136−43.
36. De Keulenaer GW, Brutsaert DL. Diastolic heart failure: a separate disease or selection bias? Progr Cardiovasc Dis 2007;49:275−83.
37. Ouzounian M, Lee DS, Liu PP. Diastolic heart failure: mechanisms and controversies. Nat Clin Pract Cardiovasc Med 2008;5:375−86.
38. Martinez DA, Guhl DJ, Stanley WC, Vailas AC. Extracellular matrix maturation in the left ventricle of normal and diabetic swine. Diabetes Res Clin Pract 2003;59:1−9.
39. Streeter DD Jr, Vaishnav RN, Patel DJ, Spotnitz HM, Ross J Jr, Sonnenblick EH. Stress distribution in the canine left ventricle during diastole and systole. Biophys J 1970;10:345−63.
40. Henein MY, Gibson DG. Long axis function in disease. Heart 1999;81: 229−31.
41. Belghiti H, Brette S, Lafitte S, Reant P, Ricard F, Serri K, et al. Automated function imaging: a new operator-independent strain method for assessing left ventricular function. Arch Cardiovasc Dis 2008;101:163−9.