ORIGINAL ARTICLE

Utility of Phase Standard Deviation and Histogram Bandwidth, Derived from Phase Analysis, as Clinical Indicators of Heart Failure

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Received: June 6, 2017/Revised manuscript received: August 1, 2017/Accepted: August 17, 2017
J-STAGE Advance published: November 17, 2017
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Abstract

***Purpose*: "Heart Function View (HFV)" is a software that performs phase analysis as well as functional assessment of the left ventricle (LV) using myocardial perfusion single-photon emission computed tomography (SPECT) (MPS). Phase analysis-derived phase standard deviation (PhSD) and histogram bandwidth (PhHB) are good indices for detecting LV dyssyncrony. We aimed to examine whether PhHB and/or PhSD (PhHB/PhSD) are useful clinical indicators that reflect the severity of heart failure (HF) in comparison with the LV ejection fraction (EF).**

***Methods*: Patients underwent ^{99m}Tc-tetrofosmin quantitative gated MPS including treadmill exercise. In HFV analyses, patients with induced ischemia were excluded. Phase and time-volume curve analyses were performed using HFV (n=66).**

***Results*: PhHB/PhSD correlated with LV end-diastolic volume (EDV), end-systolic volume (ESV), the first-third filling fraction (1/3FF), and peak filling rate (PFR) as well as echocardiography tissue Doppler-derived E/e' as hemodynamic parameters of HF severity. LVEF also correlated with these hemodynamic parameters, except for 1/3FF. PhHB/PhSD positively correlated with log BNP as a neurohumoral marker of HF severity. LVEF negatively correlated with log BNP. PhHB/PhSD negatively correlated with exercise capacity as physiological indicators of HF severity, whereas LVEF did not. PhHB/PhSD were significantly greater in patients receiving cardiac resynchronization therapy (CRT, n=6) than in non-CRT patients (n=66), whereas LVEF were lower.**

***Conclusion*: PhHB/PhSD, similar to LVEF, are useful clinical indicators for evaluating HF severity. However, the clinical significance of LVEF and PhHB/PhSD differ. Thus, a phase analysis may additively offer useful information for the management of HF.**

Keywords: Heart failure, Myocardial perfusion SPECT, Phase analysis
Ann Nucl Cardiol 2018；4（1）：11−22

Heart failure (HF) is a major growing public health problem in most industrialized countries (1, 2), among which Japan is now included. It is estimated that there are approximately 1-2 million patients with HF and nearly 130 per 100,000 individuals die of heart disease each year, which is closely related to the rapid aging of the Japanese population (3, 4). The left ventricle (LV) undergoes tonic structural and functional changes with physiological aging that include increases in wall thickness and chamber diameter, concentric remodeling, and increased mass; these result in cardiac insufficiency (5). However, these changes do not necessarily occur equally in the cardiac wall. Furthermore, lifestyle- or

doi: 10.17996/anc.17-00026

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aging-related diseases such as hypertension, ischemic heart disease, and heart conduction disorders have been shown to modify cardiac changes, particularly in elderly patients (6, 7). When asymmetric wall hypertrophy, localized wall motion abnormalities due to coronary artery disease (CAD), or conduction disturbances such as bundle branch blocks, occur, these changes may cause regional discordance in contractility. When LV regional discordance or dyssynchrony is induced, it may reduce pumping efficiency, resulting in a decrease in the LV ejection fraction, even if myocardial energy metabolism is maintained. Recent studies reported that phase analysis-derived phase standard deviation (PhSD) and histogram bandwidth (PhHB) are good indices for detecting LV dyssynchrony (8-10). These parameters were shown to be useful for predicting responses to cardiac resynchronization therapy (CRT) (11, 12).

"Heart Function View (HFV)" is a software that performs phase analysis as well as functional assessment of the LV from myocardial perfusion single-photon emission computed tomography (SPECT) (MPS) (13). This program provides information on the distribution of time intervals when various regions of the LV wall start to contract. PhHB and/or PhSD (PhHB/PhSD) may be automatically calculated. LV dimensions, and systolic and diastolic functional parameters (F(x)) may also be obtained using HFV,

The aim of the present study was to examine whether phase analysis-derived PhHB/PhSD are useful as clinical indicators of HF severity. To achieve this aim, we examined the relationships between PhHB/PhSD and LV dimensions [end-diastolic volume (EDV), end-systolic volume (ESV)], diastolic F(x) [the first-third filling fraction (1/3FF), peak filling rate (PFR), and ultrasound echocardiography (UCG) tissue Doppler diastolic functional indicator E/e' (14,15)], plasma B-type natriuretic peptide (BNP) concentrations (16), and treadmill exercise capacity in comparison with the LV ejection fraction (EF) as a conventional indicator of HF severity. Furthermore, LVEF and PhHB/PhSD values were compared in patients with and without CRT.

Methods

Subjects for the HFV analysis

Subjects comprised patients who underwent MPS between July 1, 2004 and February 28, 2013 for the examination of suspected or diagnosed heart disease in the hospital of the Shiga University of Medical Science. Seventy-two patient datasets were analyzed from available data sources using HFV. Inclusion criteria were as follows: (a) ^{99m}Tc-tetrofosmin quantitative gated MPS with 16-framing data acquisition was performed, (b) a stress test was conducted using the Bruce protocol (17) treadmill exercise, and (c) no ischemic findings were detected. Because the aim of the present study was to examine the utility of a phase analysis of HF, patients with induced ischemia were decided to be excluded by two cardiologists. Basic criteria for CRT were advanced heart failure (New York Heart Association [NYHA] functional class III-IV) despite appropriate medical therapy, reduced systolic LV function (LVEF ≤ 35%), and a prolonged QRS duration (≥120 ms due to a left bundle branch block [LBBB]; or ≥ 150 ms due to a non-LBBB and sinus rhythm) in our hospital, although we followed the Japan Circulation Society guidelines for non-pharmacotherapy of cardiac arrhythmias. Informed consent was obtained from the patients studied. Main analyses were performed on patients with no CRT (n=66). Of these patients, six had LBBB. LVEF and PhHB/PhSD in patients with CRT (n=6) were compared with those in patients without CRT in the CRT study only (Fig. 7, which will be discribed later). Patient characteristics are shown in Table 1.

Stress MPS

A symptom-limited treadmill exercise test was performed. In the Bruce protocol (17), walking started at a speed of 1.7 m/hour at a grade of 10%, and the speed and grade increased every 3 minutes. The metabolic equivalents (METs) of workload were calculated using the following formula: METs=[1.11+0.016X (exercise time in seconds)]. A dose of 296 MBq of ^{99m}Tc-tetrofosmin (Nihon Medi-Physics Co., Ltd., Hyogo, Japan) was intravenously administered when maximal exercise was attained. Thirty minutes after the first tracer injection, electrocardiogram (ECG)-gated MPS images were acquired (stress images). Three hours after the first tracer injection, a dose of 740 MBq of ^{99m}Tc-tetrofosmin was intravenously re-administered. Thirty minutes after the second tracer injection, ECG-gated MPS images were acquired (rest images). A three-headed rotating gamma camera (GCA-9300A/UI, Toshiba Medical, Tokyo, Japan) equipped with a low-energy, high resolution collimator (system resolution, FWHM: full width at half maximum 7.7 mm) and the medical image processer GMS-5500 A/UI (Toshiba Co., Tokyo, Japan) was employed for image processing. The gamma camera rotated, collecting 60 projections over 360°. Projection data were reconstructed into 64X64 matrix images using the filter back projection method with a Butterworth filter (order 8, cut-off 0.4 cycles/cm) and ramp filter. The cardiac cycle was divided into 16 frames, with an average R-R interval of ±15% being allowed for gating. All 72 patients showed non-ischemic findings. Datasets from rest images were used in the following analyses (Fig. 6 included data analyses from stress images). The "HFV" (version 1.0, Nihon Medi-Physics Co., Ltd.) software was used to process short-axis tomograms in order to assess the position of the inner LV edge (13). In this program, Fourier curve fitting was performed, and LVF(x) was automatically calculated from the time-volume curve and

Table 1 Patient characteristics

Patient characteristics	non CRT		CRT
n	66		6
Male/Female	55/11		2/4
Age (years)	65 ± 11		67 ± 15
BMI (kg/m2)	23.2 ± 5.3		21.0 ± 4.9
Heart rate (b.p.m.)	65 ± 11		65 ± 9
QRS duration (ms)	105 ± 22		147 ± 20
LVEF (%)	61.4 ± 14.9		37.1 ± 14.6
PhHB (degrees)	55.0 ± 31.0		102.3 ± 33.3
PhSD	16.8 ± 11.0		30.7 ± 8.9
Exercise (METs)	8.4 ± 2.2		7.0 ± 2.2
End point (n)	Leg fatigue (34)	Dyspnea (22)	Leg fatigue (3)
	Chest symptoms (5)		Dyspnea (2)
	General fatigue(3)	Dizziness (2)	General fatigue (1)
Diseases (n)	Suspected ischemic heart disease (26)		Dilated cardiomyopathy (4)
	Old myocardial infarction (13)		Cardiac sarcoidosis (1)
	Dilated cardiomyopathy (5)		Others (1)
	Hypertensive heart disease (5)		
	Valvular disease (4)		
	Cardiac sarcoidosis (3)		
	ARVC (1)		
	Others (9)		

ARVC: Arrhythmogenic right ventricular cardiomyopathy, BMI: body mass index, CRT: cardiac resynchronization therapy, LVEF: left ventricular ejection fraction, PhHB: phase analysis-derived histogram bandwidth, and PhSD: phase standard deviation

its differentiation curve. As systolic F(x), LVEF was obtained, and as diastolic F(x), the first-third filling fraction (1/3FF) and peak filling rate (PFR) were calculated. The "HFV" software also provided information on the distribution of time intervals when various regions of the LV wall started to contract. As shown in Fig. 1, this program generated a phase distribution (0 to 360°) spanning the R-R interval, from which PhHB/PhSD were calculated. PhHB included 95% of the elements of the phase distribution, while PhSD exhibited the standard deviation (SD) of the phase distribution.

Ultrasound echocardiography

Ultrasound machines (Vivid E9 [GE Medical Systems, Milwaukee, WI, USA]; Philips iE33 [Phillips Medical Systems, Andover, MA, USA]) were used to measure the delay between the motion of the septum and left posterior wall (septal-to-posterior wall motion delay, SPWMD) as an UCG marker of dyssynchrony (18) in color Doppler M-mode images. Furthermore, in Doppler methods, the ratio of the E diastolic mitral inflow velocity to septal e' diastolic tissue Doppler mitral annular velocity (E/e') was calculated. E/e' was estimated as a representative UCG indicator of LV diastolic function (14, 15, 19).

Statistical analysis

Data are expressed as the mean ± SD. The relationships between functional parameters and exercise duration were examined by a linear regression analysis. Single comparisons were performed with the Student's paired or unpaired *t*-test. A value of $p<0.05$ was considered to be significant.

Results

Relationship between age or QRS duration and PhHB/PhSD/LVEF

As shown in Fig. 1, there were no correlations between age and PhHB/PhSD in the 66 patients studied. Positive linear correlations were observed between the ECG QRS duration and PhHB/PhSD. In addition, there were no correlations between age and LVEF in 66 patients (figure not shown). A negative linear correlation was found between the ECG QRS duration and LVEF ($r=-0.65$, $p<0.0001$, figure not shown).

Relationship between UCG-derived SPWMD and PhHB/PhSD

Fig. 2 shows the relationship between SPWMD and PhHB/PhSD in 16 patients. SPWMD positively correlated with PhHB/PhSD.

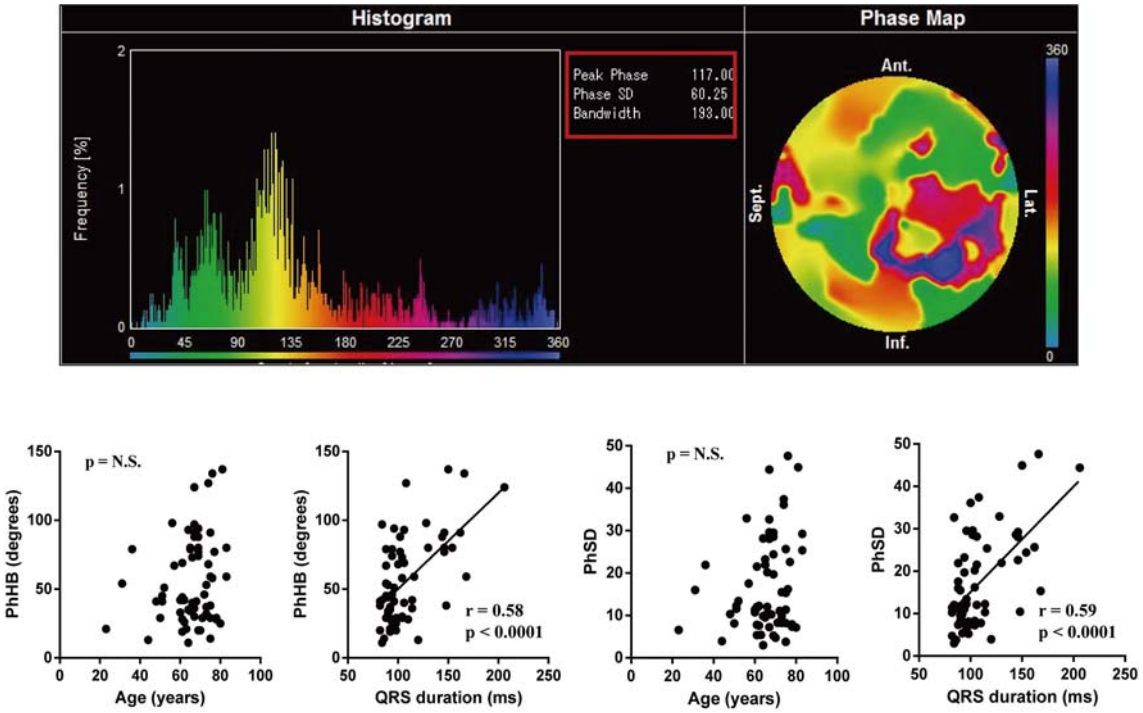

Fig. 1

Example of a phase histogram (**left**) and phase polar map (**right**) by the "Heart Function View" phase analysis. Automatically calculated histogram bandwidth (PhHB) and phase standard deviation (PhSD) values are shown in the midportion (**top panel**).

No correlations among age, PhHB, and PhSD, and positive correlations among the electrocardiogram (ECG) QRS duration, PhHB, and PhSD (**bottom panel**). Datasets from rest images were used in this figure.

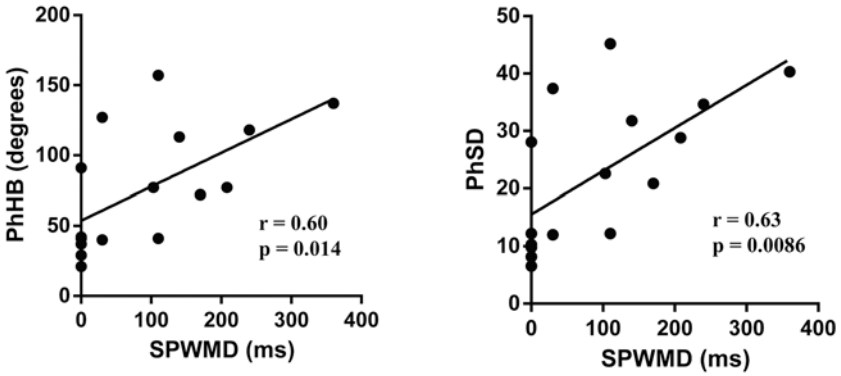

Fig. 2

Correlations of ultrasonic echocardiography (UCG) septal-to-posterior wall motion delay (SPWMD) with gated SPECT phase analysis-derived histogram bandwidth (PhHB, **left**) and phase standard deviation (PhSD, **right**). Datasets from rest images were used in this figure.

Relationship between LVEDV/LVESV and LVEF/PhHB/PhSD

Fig. 3 shows correlations between LVEDV/LVESV and LVEF/PhHB/PhSD in 66 patients. A negative linear correlation was observed between LVEF and LVEDV/LVESV. A positive linear correlation was found between PhHB and LVEDV/LVESV. A positive linear correlation was also noted between PhSD and LVEDV/LVESV.

Relationship between LVEF/PhHB/PhSD and diastolic F (x) 1/3FF /PFR

Fig. 4 shows correlations between LVEF/PhHB/PhSD and 1/3FF /PFR in 66 patients. LVEF did not correlate with 1/3FF, but positively correlated with PFR. PhHB showed a negative linear correlation with 1/3FF /PFR. PhSD also negatively correlated with 1/3FF /PFR. Furthermore, even when examined in patients with normal LV systolic function only (LVEF ≥50%, n=55), these correlations were similar: LVEF did not

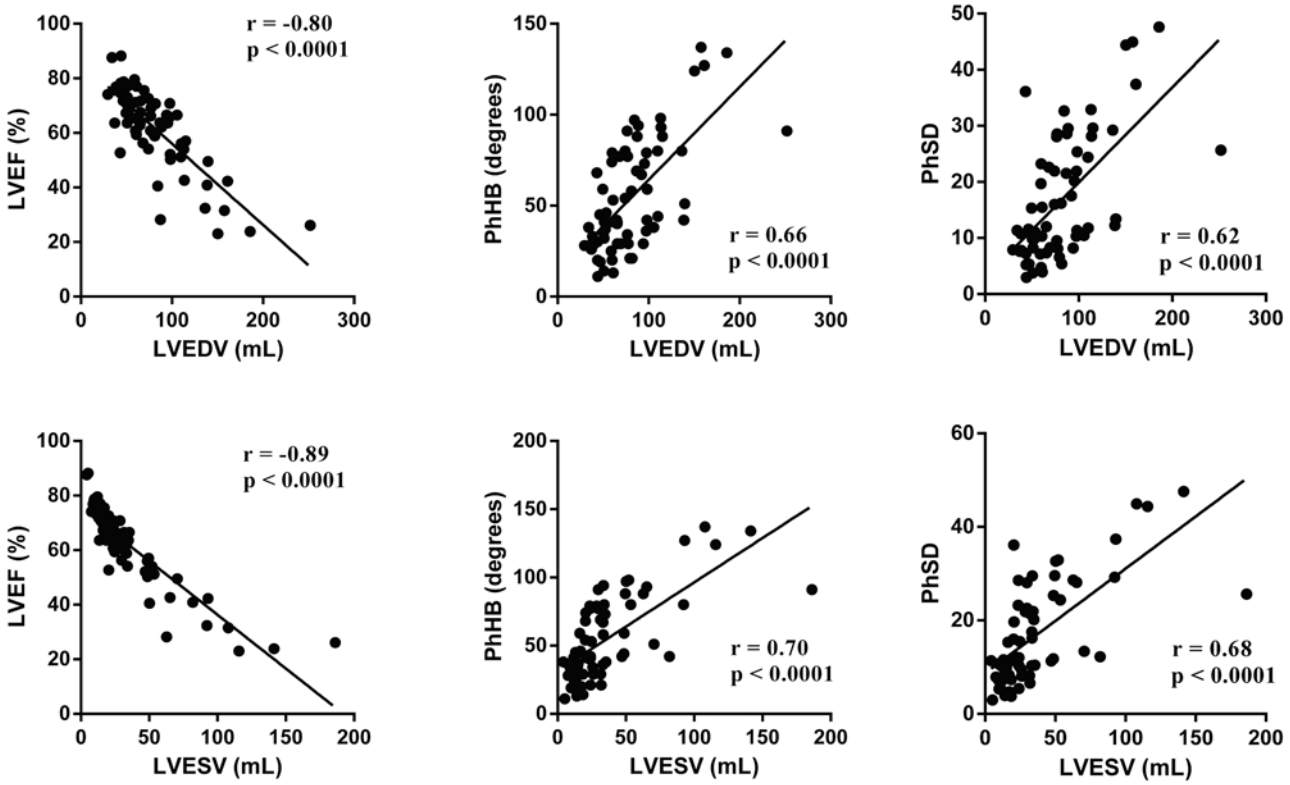

Fig. 3

Correlations of left ventricular (LV) end-diastolic volume (LVEDV, **top**) or end-systolic volume (LVESV, **bottom**) with LV ejection fraction (LVEF, **left**), phase analysis-derived histogram bandwidth (PhHB, **middle**), and phase standard deviation (PhSD, **right**). Datasets from rest images were used in this figure.

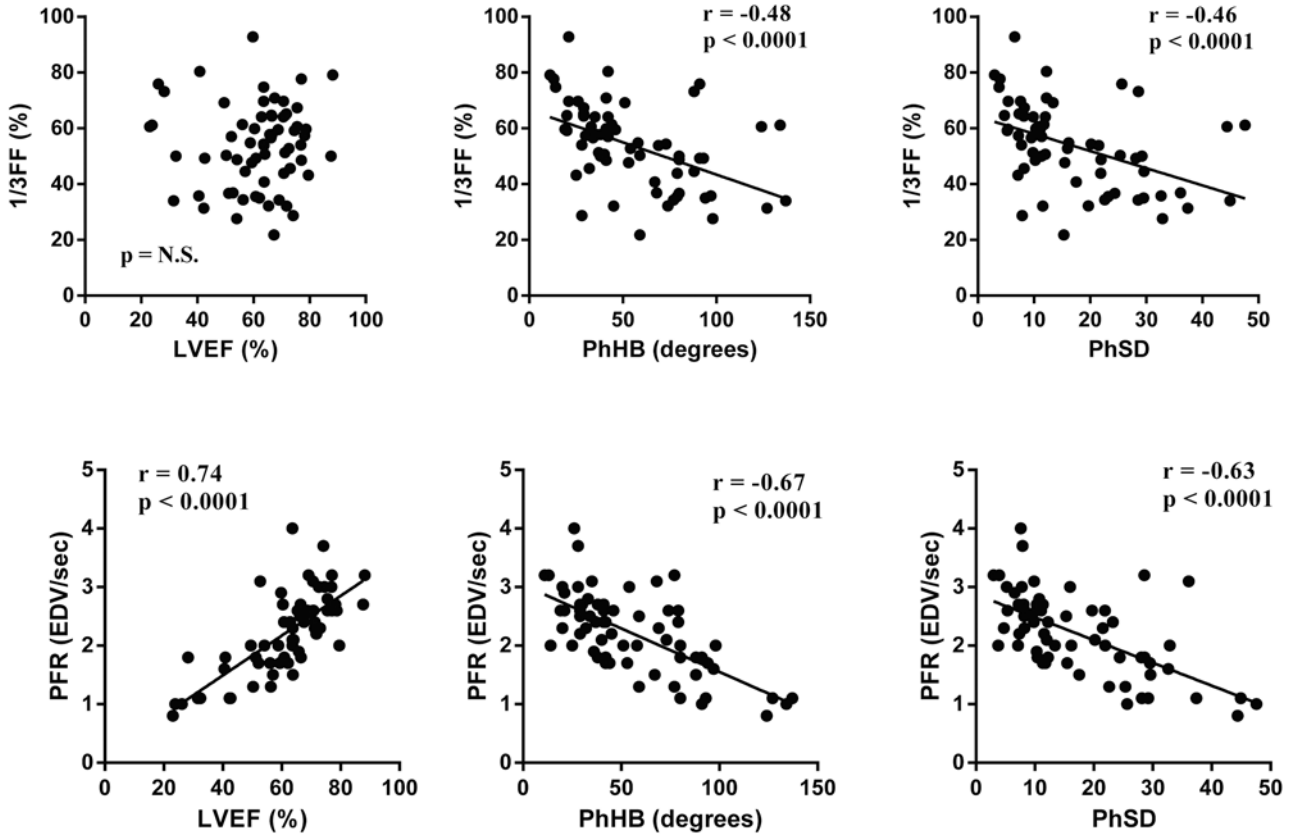

Fig. 4

Correlations of left ventricular ejection fraction (LVEF, **left**), phase analysis-derived histogram bandwidth (PhHB, **middle**), and phase standard deviation (PhSD, **right**) with the diastolic functional parameter first-third filling fraction (1/3FF, **top**) or peak filling rate (PFR, **bottom**). Datasets from rest images were used in this figure.

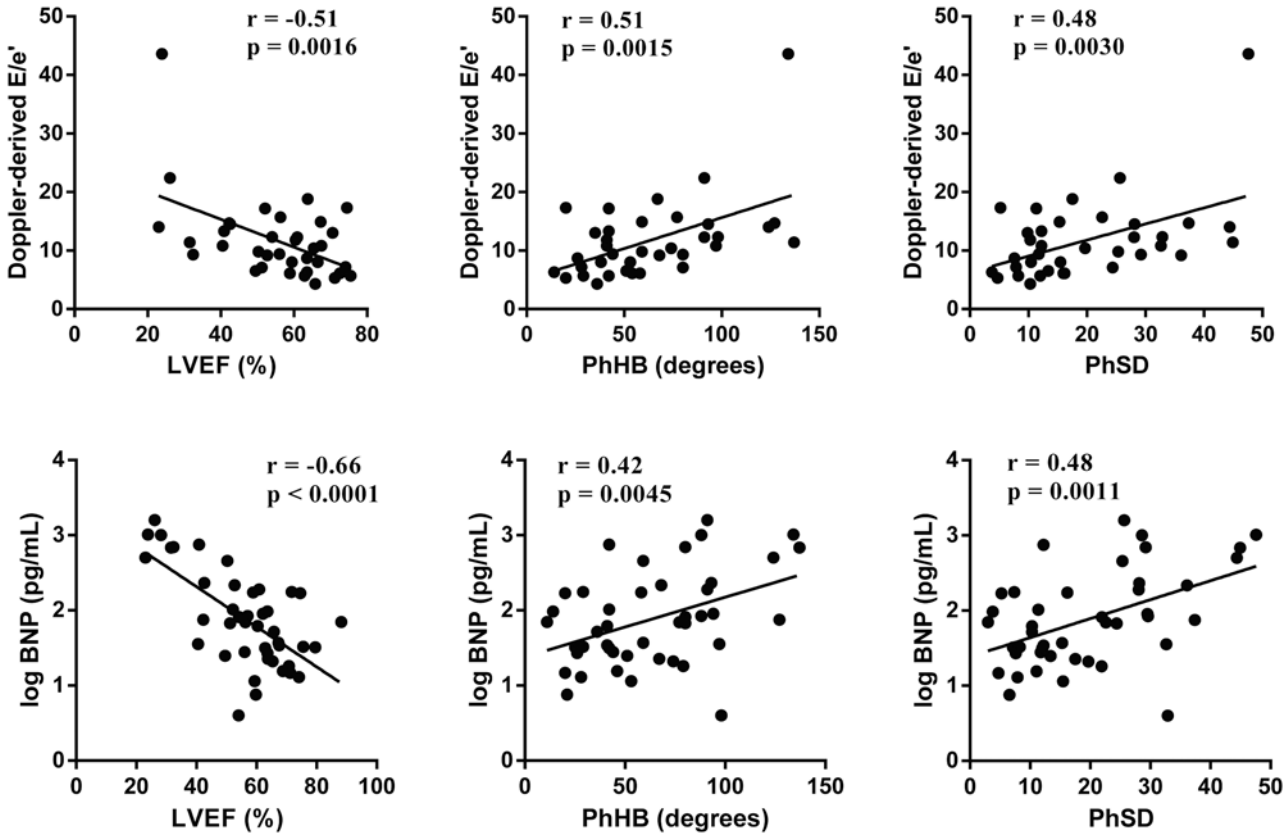

Fig. 5
Correlations of left ventricular ejection fraction (LVEF, **left**), phase analysis-derived histogram bandwidth (PhHB, **middle**), and phase standard deviation (PhSD, **right**) with the ultrasonic echocardiography diastolic parameter tissue Doppler-derived E/e' (**top**) or biochemical neurohumoral heart failure marker plasma BNP concentrations in logarithmic scales (**bottom**). Datasets from rest images were used in this figure.

correlate with 1/3FF, but positively correlated with PFR (r= 0.53, p<0.0001); PhHB showed a negative linear correlation with 1/3FF (r = -0.69, p < 0.0001) and PFR (r = -0.46, p = 0.0004); PhSD also negatively correlated with 1/3FF (r=-0.65, p<0.0001) and PFR (r=-0.37, p=0.0048) (figure not shown).

Relationship between LVEF/PhHB/PhSD and other clinical parameters, tissue Doppler-derived E/e' /plasma BNP concentrations

Fig. 5 shows correlations between LVEF/PhHB/PhSD and tissue Doppler-derived E/e' (n=36)/logarithmic-transformed plasma BNP concentrations (n = 43). LVEF negatively correlated with E/e'/log BNP. PhHB positively correlated with E/e'/log BNP. PhSD also positively correlated with E/e'/log BNP.

Relationship between LVEF/PhHB/PhSD and exercise capacity

Fig. 6 shows correlations between LVEF/PhHB/PhSD and treadmill exercise capacity in 66 patients. No correlation was observed between LVEF and exercise capacity. PhHB negatively correlated with exercise capacity. PhSD also negatively correlated with exercise capacity. As shown in Fig. 6, LVEF significantly decreased (-4%) after exercise stress (61.4 ± 14.9% at rest and 59.1 ± 15.2% after stress, p<0.0001). PhHB/PhSD both siginificantly increased after exercise stress by 30% and 32%, respectively (55.0 ± 31.0 degrees at rest and 71.6 ± 33.4 degrees after stress in PhHB, p<0.0001; 16.8 ± 10.2 at rest and 22.2 ± 11.8 after stress in PhSD, p<0.0001). There was no significant difference between heart rate at rest (65 ± 11 b.p.m.) and that after exercise (67 ± 11 b.p.m.) in these 66 patients.

Comparison of LVEF/PhHB/PhSD between patients with and without CRT

Fig. 7 shows differences between LVEF/PhHB/PhSD values in 72 patients with (n=6) and without CRT (n=66). Six patients received CRT before the MPS study (post-CRT). Patient characteristics are shown in Table 1. In the present study, most of the MPS study was performed after CRT in order to avoid the cardiac risk associated with exercise stress. Of the 66 patients, two, however, received CRT within 30 days after the MPS study. Six patients received implantable cardioverter defibrillator (ICD) therapy. LVEFs were significantly lower in patients with CRT than in those without. PhHB/PhSD were both significantly greater in patients with

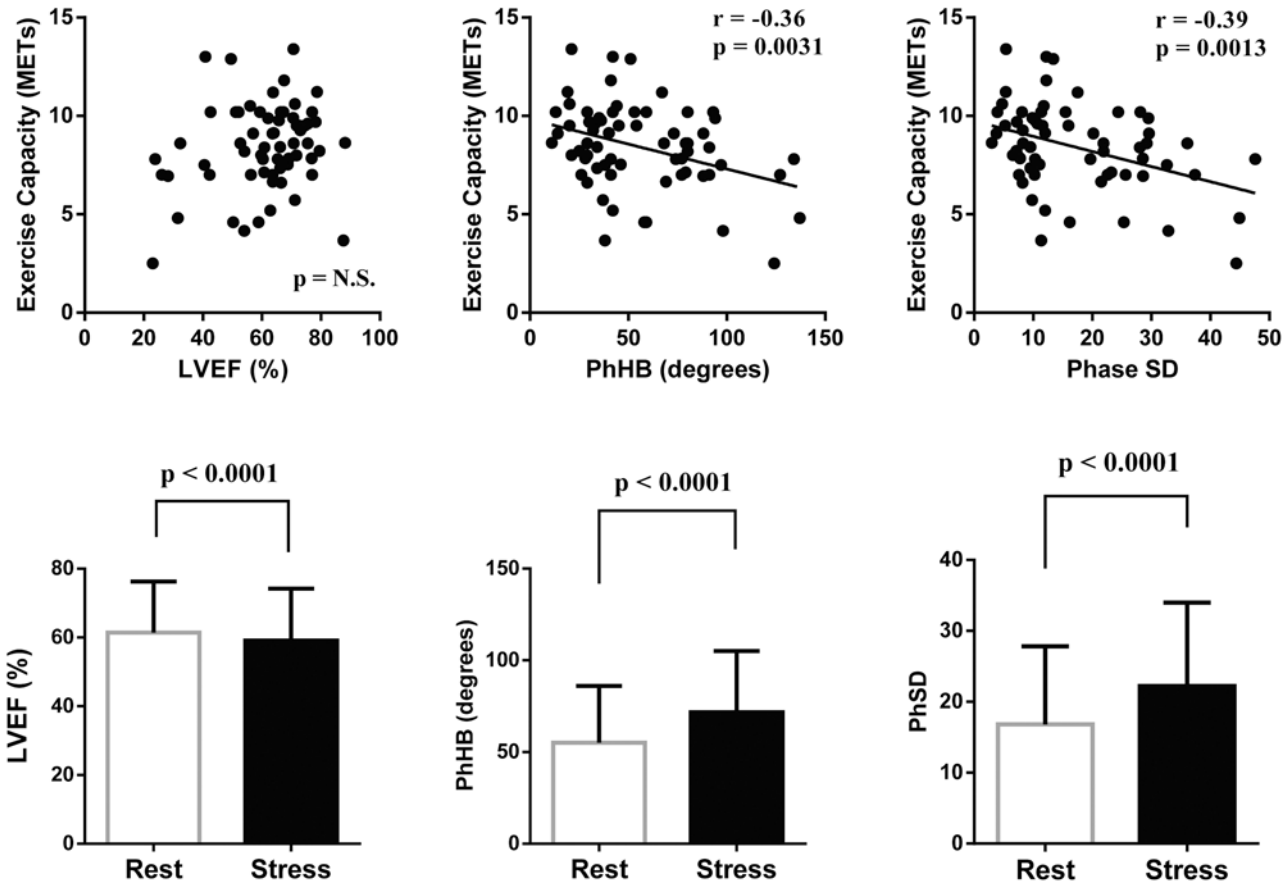

Fig. 6

Correlations of left ventricular ejection fraction (LVEF, **left**), phase analysis-derived histogram bandwidth (PhHB, **middle**), and phase standard deviation (PhSD, **right**) with treadmill exercise capacity (**top**). Changes in the values of LVEF (**left**), PhHB (**middle**), and PhSD (**right**) at rest and after exercise stress (**bottom**). Datasets from rest and stress images were used in this figure.

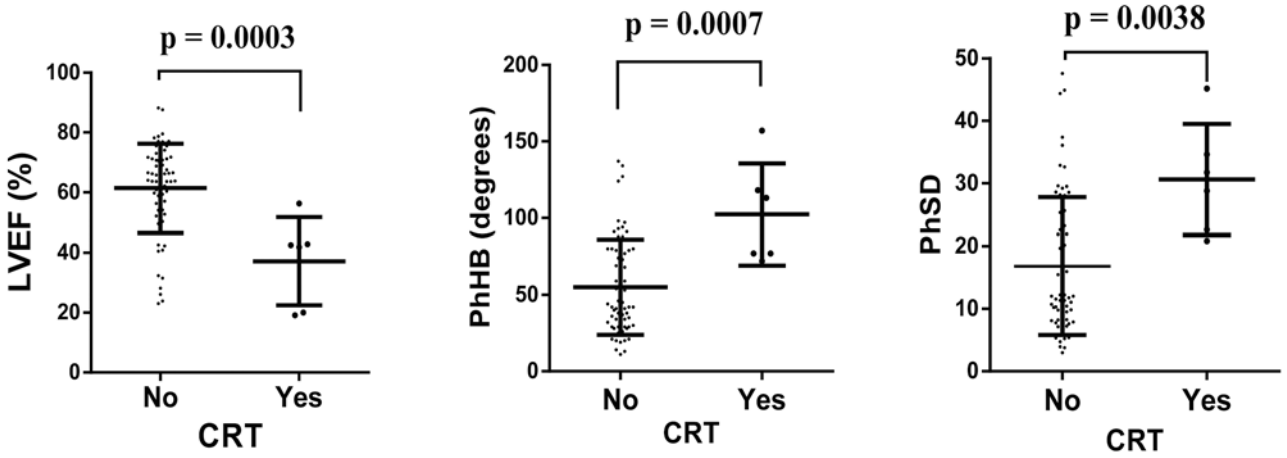

Fig. 7

Differences between the left ventricular ejection fraction (LVEF, **left**), phase analysis-derived histogram bandwidth (PhHB, **middle**), and phase standard deviation (PhSD, **right**) values in patients with (**Yes**) and without (**No**) cardiac resynchronization therapy (CRT) during the myocardial perfusion SPECT study. Horizontal lines: mean ± SD. Small dots indicate individual data. Datasets from rest images were used in this figure.

CRT than in those without. Even when the two patients who received CRT after the MPS study were excluded, these differences were significant (EF, p=0.0001; PhHB, p=0.0001; PhSD, p=0.0020 by Student's *t*-test).

Relationship between LVEF and PhHB/PhSD

The relationship between LVEF and PhHB/PhSD was examined. There was a negative correlation between LVEF and PhHB (r = -0.76, p < 0.0001, n = 66, figure not shown).

There was also a negative correlation between LVEF and PhSD (r=-0.77, p<0.0001, n=66, figure not shown).

Discussion

Study results

In the present study, we examined the utility of PhHB/PhSD as clinical indicators that reflect HF severity. From a clinical viewpoint, the pathology of HF may be characterized by the following points: (a) hemodynamic changes, such as cardiac dilatation and decreased systolic and diastolic functions; (b) neurohumoral changes including high plasma levels of BNP and catecholamines; and (c) exercise intolerance due to symptoms such as shortness of breath and fatigue. Based on these viewpoints, we examined the relationships between PhHB/PhSD and (a) LVEDV, ESV, 1/3FF, PFR, and tissue Doppler E/e'; (b) logarithmic-transformed BNP concentrations; and (c) treadmill exercise capacity, in comparison with LVEF as a conventional HF indicator. PhHB and PhSD showed similar behaviors, as shown above and below, and thus, were expressed as PhHB/PhSD in many cases in the present study. PhHB/PhSD correlated with LVEDV, ESV, 1/3FF, PFR, and tissue Doppler E/e'. LVEF also correlated with LVEDV, ESV, PFR, and E/e', but not with 1/3FF. PhHB/PhSD correlated with log BNP, as did LVEF. PhHB/PhSD negatively correlated with treadmill exercise capacity, whereas LVEF did not. Although associations between LVEF and PhHB/PhSD were also observed, the clinical significance of LVEF and PhHB/PhSD differed, despite having similar properties.

Relationship between age and PhHB/PhSD

As described above, aging may induce LV structural and functional changes (7). We initially examined the relationship between age and PhHB/PhSD. In the patients studied, no correlation was found between age and PhHB/PhSD. Disease itself rather than aging appears to influence PhHB/PhSD. Furthermore, there was no correlation between age and LVEF.

Relationship between the QRS duration and PhHB/PhSD

ECG is the most readily available non-invasive test for the diagnosis of heart disease. LV systole begins at the QRS complex on ECG. Normal ECG is a marker for normal LV systolic function. In contrast, widening of the QRS complex is associated with attenuated LV systolic function (20, 21). Murkofsky et al. identified a prolonged QRS duration as a specific indicator of decreased LV systolic function using radionuclide ventriculography (20). In the present study, a positive correlation was observed between the QRS duration and PhHB/PhSD. These results suggest that PhHB/PhSD, similar to the QRS duration, are indicators for assessing LV systolic dysfunction.

Comparison with PhHB/PhSD from other analysis software programs and SPWMD as a dyssynchrony parameter of UCG

Henneman et al. showed that PhHB/PhSD from a phase analysis of gated MPS by Emory Cardiac Toolbox (ECTb) correlated with LV dyssynchrony assessed by UCG using tissue Doppler imaging (TDI), and demonstrated that these parameters were useful for predicting CRT responses (8). Furthermore, Boogers et al. indicated that PhHB/PhSD from a phase analysis on gated MPS using QGS software correlated with LV dyssynchrony assessed by TDI and enabled responses to CRT to be accurately predicted (12). However, in a study by Nakajima et al., PhHB/PhSD calculated by HFV did not correlate with those by ECTb in 69 subjects (22). LV dyssynchrony parameters from HFV correlated with those from another analysis program, cardioREPO (cREPO). Regarding the normal values of PhHB/PhSD in that study, there appeared to be similarities between ECTb and cREPO and between QGS and HFV. Thus, differences among phase dyssynchrony parameters were reported in the four analysis software programs. Hence, here we examined the relationship between HFV-derived PhHB/PhSD and septal-to-posterior wall motion delay (SPWMD) as an UCG marker of LV dyssynchrony. SPWMD is a useful UCG index for the assessment of responses to CRT (18). As expected, a correlation was observed between PhHB/PhSD and SPWMD in the present study.

Relationship between LVEDV/LVESV and PhHB/PhSD

In the present study, LVEDV/LVESV positively correlated with PhHB/PhSD. LVEDV/LVESV negatively correlated with LVEF. In general, the bigger cardiac size is, the worse cardiac function becomes (23). Therefore, increases in PhHB/PhSD indicate LV structural and functional changes.

Relationship with LV diastolic F (x) 1/3FF/PFR/tissue Doppler E/e'

In the present study, PhHB/PhSD correlated with LV diastolic F(x) 1/3FF/PFR/tissue Doppler E/e'. LVEF correlated with PFR/E/e', but not with 1/3FF. As described earlier, phase images show the distribution of time intervals when various regions of the LV wall start to contract (8-10, 24). Therefore, PhHB/PhSD may be regarded as systolic F(x) (i.e., indices of systolic dyssynchrony). LVEF is a representative systolic F(x). The results of the present study suggest that LVEF/PhHB/PhSD are associated with diastolic F(x). However, LVEF did not correlate with 1/3FF. The diastolic characteristics of the heart comprise two aspects: relaxation and wall stiffness (25). The former component, relaxation, is basically an active, energy-dependent process and is assessed during early diastole (the first third of diastole). In contrast, the

latter component, ventricular stiffness or compliance, is a passive change in ventricular volume for a given change in pressure and is measured at end-diastole. 1/3FF reflects the former component. Thus, abnormalities in PhHB/PhSD may be related to impaired LV relaxation. Concerning LVEF, even if LVEF is normal, heart failure is known to be caused by diastolic dysfunction, which is so-called "diastolic heart failure (DHF)" (26). In this case, HF severity cannot be judged by LVEF. The evaluation by PhHB/PhSD from HFV may be useful for DHF. In an UCG study, Wang et al. reported that systolic dyssynchrony was observed in 33% of DHF patients, while diastolic dyssynchrony was detected in 58% (27). Boogers et al. reported that a diastolic phase analysis on gated MPS revealed a good correlation with TDI for the assessment of LV diastolic dyssynchrony (28). Theoretically, the assessment of PhHB/PhSD with diastolic phase analysis, not systolic phase analysis, of gated MPS is warranted for DHF. However, presently, it seems difficult to obtain useful results by applying diastolic phase analysis to ordinary MPS examination because of scattered data values. Therefore, further studies are warranted to confirm the usefulness of a diastolic phase analysis using gated MPS.

Relationship between LVEF/PhHB/PhSD and log BNP

Pasma BNP concentrations are a reliable biochemical marker of HF severity (16). Furthermore, BNP is a prognostic marker of chronic HF (29). In the present study, LVEF strongly correlated with log BNP, while the correlation between PhHB/PhSD and log BNP was relatively weak. Plasma BNP concentrations appear to be closely related with cardiac pumping function, and the low LVEF values obtained by 3-dimensional analyses may accurately represent the cardiac pumping dysfunction. On the other hand, increased PhHB/PhSD did not necessarily mean cardiac pumping failure. In no-symptom patients with a bundle branch block, global cardiac pumping function may be preserved. Since this study included these patients, the relationship between log BNP and PhHB/PhSD was weaker than that with LVEF. Further studies are needed to establish whether PhHB/PhSD have prognostic value in chronic HF.

Relationship with exercise capacity

In the present study, PhHB/PhSD negatively correlated with treadmill exercise capacity as a physiological indicator of HF, whereas LVEF did not. The reason for this is unclear; however, previous studies indicated that LV diastolic dysfunction rather than systolic function is associated with exercise intolerance (30, 31), and PhHB/PhSD are related to diastolic function as described above. Although the mechanisms underlying the relationship between diastolic function and exercise capacity have not yet been elucidated in detail, previous studies provided some explanations (30-37). In tachycardia induced by exercise, abnormalities in LV diastolic relaxation and filling may limit the ability to achieve adequate cardiac output, even if systolic function is preserved (32). An excessive increase in pulmonary capillary wedge pressure during exercise may be the main cardiac cause of exertional dyspnea (30, 33), and abnormalities in UCG tissue Doppler-derived diastolic F (x) are related to elevated pulmonary capillary wedge pressure (34, 35). Moreover, LV diastolic dysfunction may be related to skeletal muscle weakness (36), particularly inspiratory muscle weakness (37), causing dyspnea and tachypnea during exercise. We discussed these matters in our previous study (31).

Changes in LVEF/PhHB/PhSD after exercise

In the present study, LVEF decreased by no more than 4% after exercise. In contrast, PhHB/PhSD increased by no less than 30%. Because all the patients studied showed non-ischemic findings in exercise testing, these changes were considered unrelated to myocardial ischemia. Previous studies suggested that a change in LV systolic or diastolic function after exercise is a useful marker of the occurrence of myocardial ischemia (38, 39). Stoddard et al. investigated 101 patients who underwent a ^{201}Tl tomographic treadmill exercise test and Doppler echocardiography, and reported that LVEF and diastolic filling were both impaired in patients with a reversible thallium defect for more than 2 hours after exercise (38). We also performed ^{99m}Tc-tetrofosmin quantitative gated SPECT including a treadmill exercise test in 39 patients, and showed that LVEF, 1/3FF, and PFR were reduced in patients with a reversible perfusion defect suggesting ischemia for more than 3 hours after exercise stress (39). Regarding PhHB/PhSD, Tanaka et al. reported that changes in PhHB/PhSD after adenosine triphosphate (ATP) stress were useful for the detection of multivessel CAD by performing multidirectional coronary angiography and a phase analysis with ^{99m}Tc-sestamibi quantitative gated SPECT (40). However, our results suggested that changes in PhHB/PhSD after exercise are not useful as clinical indicators for the detection of ischemia because PhHB/PhSD markedly increased in non-ischemic cases. Aljaroudi et al. (41) examined the effects of a tracer dose on phase-analysis indices, and concluded that PhSD derived from gated SPECT with low-dose tracer (370-555 MBq ^{99m}Tc-tetrofosmin) was higher than the corresponding index derived from high-dose gated SPECT (～1110-1665 MBq), irrespective of LVEF, analysis software, the type of stress test, or BMI. This finding is consistent with our result showing that PhHB/PhSD from low-dose stress gated SPECT (296 MBq) were higher than those from high-dose rest gated SPECT (740 MBq), independently of induced ischemia. Thus, dose differences may, at least partially, account for the ～30%

change observed in PhHB/PhSD after exercise.

As described above, LVEF slightly, but significantly decreased (-4%) after exercise in our study. Previously, we examined whether change in LVEF during stress testing assessed using MPS, was useful as an indicator of myocardial ischemia (39). As a result, altered LVEF after exercise was useful for the detection of myocardial ischemia. However, similar findings were observed in some patients with cardiac dysfunction, but without detectable ischemia. Such findings were not observed in patients without LV dysfunction. Therefore, in patients with cardiac dysfunction, but without ischemia, cardiac load itself may deteriorate cardiac dysfunction. Alternatively, these patients may have ischemia that cannot be detected. Furthermore, LV dysfunction has low amplitude of wall motion, which may induce an artifact for functional or phase analysis because of limited spatial and time resolution. We discussed these matters in our previous study (39). In the present study, data obtained from patients with cardiac dysfunction might have affected the results. Further examinations are needed.

LVEF/PhHB/PhSD in patients with and without CRT

As expected in the present study, LVEFs were lower in patients with CRT than in those without, while PhHB/PhSD were greater in patients with CRT than in those without. As described earlier, most of the MPS studies were performed after CRT to avoid the cardiac risk associated with exercise stress. Nevertheless, PhHB/PhSD values in patients with CRT were still higher. Strictly speaking, PhHB/PhSD values cannot differentiate between dyssynchrony and wall motion abnormality. Moreover, these are often mixed in the dysfunctional heart. Therefore, increases in PhHB/PhSD might have been influenced by local or global wall motion abnormality.

Boogers et al. reported that a gated SPECT- derived phase analysis was useful not only for the detection of LV dyssynchrony, but also for the prediction of CRT responses (12). We did not assess the prognosis of CRT patients; therefore, further studies are needed to clarify how a phase analysis including a stress test provides prognostic information for patients receiving CRT.

Comparison with normal LVEF/PhHB/PhSD values using HFV

Normal values for LVEF/PhHB/PhSD using HFV were recently reported: LVEF 71.7 ± 6.4%, PhHB 19.9 ± 9.1 degrees, and PhSD 5.4 ± 2.5 (22). Therefore, among the patients studied, the mean LVEF was within the normal range, whereas the mean values of PhHB/PhSD were greater, and this may have influenced our results. Moreover, gender differences have been reported in these values: male, LVEF 69.5 ± 6.4%, PhHB 23.1 ± 9.5 degrees, and PhSD 6.2 ± 2.7; female, LVEF 74.0 ± 5.7%, PhHB 16.5 ± 7.2 degrees, and PhSD 4.4 ± 1.8. However, gender differences were not investigated in the present study because of the small number of patients examined. Thus, further studies are needed.

Conclusion

As clinical indicators of HF severity, the significance of LVEF and PhHB/PhSD differed despite having similar properties: (a) PhHB/PhSD rather than LVEF were more closely related to diastolic function as a hemodynamic HF indicator; (b) LVEF rather than PhHB/PhSD was more closely related to plasma BNP as a neurohumoral HF marker; and (c) PhHB/PhSD, not LVEF, were related to exercise capacity as a physiological HF indicator. Thus, an additive phase analysis may provide useful information for HF management.

Acknowledgments

We would like to thank Ms. Iguchi for providing excellent technical support.

Disclosures

In this article we have no conflicts of interest as well as sources of funding.

Abbreviations
ARVC: arrhythmogenic right ventricular cardiomyopathy
ATP: adenosine triphosphate
BMI: body mass index
BNP: B-type natriuretic peptide
CAD: coronary artery disease
cREPO: cardioREPO
CRT: cardiac resynchronization therapy
DHF: diastolic heart failure
ECG: electrocardiography/electrocardiogram
ECTb: Emory Cardiac Toolbox
EDV: end-diastolic volume
E/e': echocardiography tissue Doppler-derived E/e'
EF: ejection fraction
ESV: end-systolic volume
1/3FF: first-third filling fraction
F(x): functional parameter(s)
HF: heart failure
HFV: heart function view
ICD: implantable cardioverter defibrillator
JCS: Japan Circulation Society
LBBB: left bundle branch block
LV: left ventricle or ventricular
MPS: myocardial perfusion SPECT
PFR: peak filling rate
PhHB: phase analysis-derived histogram bandwidth
PhSD: phase analysis-derived phase standard deviation

PhHB/PhSD: PhHB and/or PhSD
PhHB/PhSD/LVEF: PhHB, PhSD and/or LVEF
QGS: quantitative gated SPECT
SPECT: single-photon emission computed tomography
SPWMD: septal-to-posterior wall motion delay
TDI: tissue Doppler imaging
UCG: ultrasound echocardiography

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References

1. Roger VL. Epidemiology of heart failure. Circ Res 2013; 113: 646-59.
2. Dunlay SM, Roger VL. Understanding the epidemic of heart failure: past, present, and future. Curr Heart Fail Rep 2014; 11: 404-15.
3. Shiba N, Shimokawa H. Chronic heart failure in Japan: implications of the CHART studies. Vasc Health Risk Manag 2008; 4: 103-13.
4. Simokawa H, Miura M, Nochioka K, et al. Heart failure as a general pandemic in Asia. Eur J Heart Fail 2015; 17: 884-92.
5. Gates PE, Tanaka H, Graves J, et al. Left ventricular structure and diastolic function with human ageing. Relation to habitual exercise and arterial stiffness. Eur Heart J 2003; 24: 2213-20.
6. Pischke CR, Weidner G, Elliott-Eller M, et al. Lifestyle changes and clinical profile in coronary heart disease patients with an ejection fraction of ≤ 40% or > 40% in the Multicenter Lifestyle Demonstration Project. Eur J Heart Fail 2007; 9: 928-34.
7. Lakatta EG, Michell JH, Pomerance A, et al. Human aging: changes in structure and function. J Am Coll Cardiol 1987; 10 (2 Suppl A): 42A-7A.
8. Henneman MM, Chen J, Ypenburg C, et al. Phase analysis of gated myocardial perfusion single-photon emission computed tomography compared with tissue Doppler imaging for the assessment of left ventricular dyssynchrony. J Am Coll Cardiol 2007; 49: 1708-14.
9. Trimble MA, Borges-Neto S, Smallheiser S, et al. Evaluation of left ventricular mechanical dyssynchrony as determined by phase analysis of ECG-gated SPECT myocardial perfusion imaging in patients with left ventricular dysfunction and conduction disturbances. J Nucl Cardiol 2007; 14: 298-307.
10. Matsuo S. Phase analysis using gated myocardial perfusion single-photon emission computed tomography imaging for evaluating cardiac dyssynchrony. Circ J 2012; 76: 1832-3.
11. Henneman MM, Chen J, Dibbets-Schneider P, et al. Can LV dyssynchrony as assessed with phase analysis on gated myocardial perfusion SPECT predict response to CRT? J Nucl Med 2007; 48: 1104-11.
12. Boogers MM, Van Kriekinge SD, Henneman MM, et al. Quantitative gated SPECT-derived phase analysis on gated myocardial perfusion SPECT detects left ventricular dyssynchrony and predicts response to cardiac resynchronization therapy. J Nucl Med 2009; 50: 718-25.
13. Nakae I, Hayashi H, Matsumoto T, et al. Clinical usefulness of a novel program “Heart Function View” for evaluating cardiac function from gated myocardial perfusion SPECT. Ann Nucl Med 2014; 28: 812-23.
14. Arques S, Roux E, Luccioni R. Current clinical applications of spectral tissue Doppler echocardiography (E/E' ratio) as a noninvasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. Cardiovasc Ultrasound 2007; 5: 16.
15. Dhutia NM, Cole GD, Willson K, et al. A new automated system to identify a consistent sampling position to make tissue Doppler and transmitral Doppler measurements of E, E’ and E/E'. Int J Cardiol 2012; 155: 394-9.
16. Wieczorek SJ, Wu AH, Christenson R, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. Am Heart J 2002; 144: 834-9.
17. Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. Ann Clin Res 1971; 3: 323-32.
18. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002; 40: 1615-22.
19. Ommen SR, Nishimura RA, Appleton CP, 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.
20. Murkofsky RL, Dangas G, Diamond JA, et al. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction. J Am Coll Cardiol 1998; 32: 476-82.
21. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol 2005; 46: 2183-92.
22. Nakajima K, Okuda K, Matsuo S, et al. Comparison of phase dyssynchrony analysis using gated myocardial perfusion imaging with four software programs: Based on the Japanese Society of Nuclear Medicine working group normal database. J Nucl Cardiol 2017; 24: 611-21.
23. Feild BJ, Russell RO Jr, Moraski RE, et al. Left ventricular size and function and heart size in the year following myocardial infarction. Circulation 1974; 50: 331-9.
24. Chen J, Garcia EV, Folks RD, et al. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. J Nucl Cardiol 2005; 12: 687-95.
25. 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.
26. Angeja BG, Grossman W. Evaluation and management of diastolic heart failure. Circulation 2003; 107: 659-63.
27. Wang J, Kurrelmeyer KM, Torre-Amione G, et al. Systolic

and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. J Am Coll Cardiol 2007; 49: 88-96.
28. Boogers MJ, Chen J, Veltman CE, et al. Left ventricular diastolic dyssynchrony assessed with phase analysis of gated myocardial perfusion SPECT: a comparison with tissue Doppler imaging. Eur J Nucl Med Mol Imaging 2011; 38: 2031-9.
29. Maisel A. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? Circulation 2002; 105: 2328-31.
30. Skaluba SJ, Litwin SE. Mechanisms of exercise intolerance: insights from tissue Doppler imaging. Circulation 2004; 109: 972-7.
31. Yoshino T, Nakae I, Matsumoto T, et al. Relationship between exercise capacity and cardiac diastolic function assessed by time-volume curve from 16-frame gated myocardial perfusion SPECT. Ann Nucl Med 2010; 24: 469-76.
32. Grewal J, McCully RB, Kane GC, et al. Left ventricular function and exercise capacity. JAMA 2009; 301: 286-94.
33. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991; 17: 1065-72.
34. Sugimoto T, Dohi K, Tanabe M, et al. Echocardiographic estimation of pulmonary capillary wedge pressure using the combination of diastolic annular and mitral inflow velocities. J Echocardiogr 2013; 11: 1-8.
35. Marchandise S, Vanoverschelde JL, D' Hondt AM, et al. Usefulness of tissue Doppler imaging to evaluate pulmonary capillary wedge pressure during exercise in patients with reduced left ventricular ejection fraction. Am J Cardiol 2014; 113: 2036-44.
36. Ventura-Clapier R, De Sousa E, Veksler V. Metabolic myopathy in heart failure. News Physiol Sci 2002; 17: 191-6.
37. Lavietes MH, Gerula CM, Fless KG, et al. Inspiratory muscle weakness in diastolic dysfunction. Chest 2004; 126: 838-44.
38. Stoddard MF, Johnstone J, Dillon S, et al. The effect of exercise-induced myocardial ischemia on postischemic left ventricular diastolic filling. Clin Cardiol 1992; 15: 265-73.
39. Nakae I, Matsuo S, Matsumoto T, et al. Clinical significance of diastolic function as an indicator of myocardial ischemia assessed by 16-frame gated myocardial perfusion SPECT. Ann Nucl Med 2008; 22: 677-83.
40. Tanaka H, Chikamori T, Hida S, et al. Diagnostic value of vasodilator-induced left ventricular dyssynchrony as assessed by phase analysis to detect multivessel coronary artery disease. Ann Nucl Cardiol 2015; 1: 6-17.
41. AlJaroudi W, Jaber WA, Cerqueira MD. Effect of tracer dose on left ventricular mechanical dyssynchrony indices by phase analysis of gated single photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 2012; 19: 63-72.

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