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ORIGINAL RESEARCH ARTICLE

Synergistic prognostication of left ventricular hypertrophy and three-dimensional mechanical dyssynchrony in heart failure

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Abstract

Aims In this study, we investigated the prognostic interplay of left ventricular hypertrophy and mechanical dyssynchrony (LVMD), both of which can be measured three-dimensionally by gated myocardial perfusion imaging (MPI), in patients with chronic systolic heart failure (HF).

Methods and results In 829 consecutive HF patients with reduced left ventricular ejection fraction less than 50%, LVMD was evaluated as a standard deviation (phase SD) of regional onset of mechanical contraction phase angles. A phase histogram was created by Fourier phase analysis applied to regional time-activity curves obtained by gated MPI. Left ventricular mass index (LVMI) was measured by Corridor 4DM version 6.0. Patients were followed up with a primary endpoint of lethal cardiac events (CE) for a mean interval of 34 months. CE were documented in 223 (27%) of the HF patients. The CE group had a greater phase SD and a greater LVMI than those in the non-CE group. Patients in the CE group had a more advanced age, greater New York Heart Association (NYHA) functional class, left ventricular cavity size, and left atrial diameter or septal E/e' and lower kidney or cardiac function than did patients in the non-CE group. Phase SD $>$ 37 and LVMI $>$ 122.7 g/m^2 were identified as optimal cut-off values by receiver operating characteristic analyses for discrimination of the most increased risk HF subgroup from others ($P < 0.0001$). When classified into four patient subgroups using both cut-off values, HF patients with phase SD $>$ 37 (LVMD) and LVMI $>$ 122.7g/m^2 had the highest CE rate among the subgroups ($P < 0.0001$). Univariate analysis and subsequent multivariate analysis with a Cox proportional hazards model showed that phase SD and LVMI were significant independent predictors of CE with hazard ratios of 1.038 (confidence interval [CI], 1.024–1.051, $P < 0.0001$) and 1.005 (CI, 1.001–1.008, $P = 0.0073$), respectively, as well as conventional clinical parameters such as age, NYHA class, estimated glomerular filtration rate (eGFR), and BNP concentration. Patients with increased phase SD and LVMI had incrementally improved prognostic values of clinical parameters including age, NYHA functional class, eGFR, and BNP with increases in the global χ^2 value: 5.9 for age; 139.5 for age and NYHA; 157.9 for age, NYHA, and eGFR; 163.9 for age, NYHA, eGFR, and BNP; 183.4 for age, NYHA, eGFR, BNP, and phase SD; and 192.5 for age, NYHA, eGFR, BNP, phase SD, and LVMI.

Conclusions Three-dimensionally assessed LVMD has independent prognostic values and can improve the risk stratification of chronic HF patients synergistically in combination with conventional clinical parameters.

Keywords Left ventricular hypertrophy; Systolic heart failure; Mechanical dyssynchrony; Cardiac mortality

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Introduction

Recent advances in pharmacological and non-pharmacological treatments have contributed to appropriate management of heart failure (HF) patients and to better outcomes. The still high morbidity and mortality rates of chronic HF, however, have been noted as important socio-economical issues. In addition to the ageing population, this is because of limited

risk stratification procedures and of difficulties in optimal selection of an invasive strategy such as device treatment and in discrimination of responders/non-responders to therapeutic interventions. There is therefore a need for a better understanding of HF pathophysiology and better prognosis assessment in the current era using various therapeutic strategies. This would involve includes reassessment of several classical but important prognostic variables such as left ventricular (LV) hypertrophy, LV ejection fraction (LVEF), New York Heart Association (NYHA) functional class, chronic kidney disease, and anaemia[1–4] in a more sophisticated manner. Despite the established prognostic efficacies of cardiac resynchronization therapy (CRT) and the current criteria,[5–7] nearly one-third of HF patients undergoing CRT cannot benefit from this device treatment,[8–11], whereas better responders to CRT may have been missed under the current guidelines. These findings show limitations of the current criteria using NYHA class, LVEF, and QRS duration (as an electrical dyssynchrony index) for the selection of a good CRT responder. LV contractile disturbance due to LV mechanical dyssynchrony (LVMD) originates in a global and inhomogeneous contraction abnormality not necessarily accompanying an electrical conduction delay. LVMD can be quantitatively evaluated using three-dimensional temporal and spatial contraction data by mathematical fitting of regional cardiac cycles with higher ordered Fourier phase analysis in gated myocardial perfusion imaging (MPI) study.[7–10] Recent investigations[4,12–15] strongly suggest the clinical advantages of assessment of LV hypertrophy and LVMD and of clarification of high-risk candidates for an invasive HF strategy.

In this study, we investigated the prognostic values and their interplays between left ventricular mass index (LVMI) and LVMD three-dimensionally evaluated for better discrimination of low-risk and high-risk HF patients undergoing contemporary treatment in association with clinical prognostic variables.

Methods

Study patients

A total of 829 consecutive patients with LVEF $<$ 50% admitted with symptomatic HF during the period from April 2011 to March 2017 were enrolled in this study. The study included 610 (73.6%) male patients. The mean age of the patients was 67.0 ± 12.1 years and the mean LVEF was 36.7 ± 9.8%. The patients were followed up until May 2018 with a mean observational interval of 34 ± 19 months. The diagnosis of HF at admission was established by clinical symptoms and signs according to the Framingham criteria including typical symptoms (palpitation, dyspnoea, or orthopnoea), neck vein distension, peripheral oedema, lung rale, S3 or S4 gallop, and tachycardia together with findings of chest X-ray and two-dimensional echocardiographic examinations such as cardiomegaly or LV enlargement, bilateral lung congestion, pleural effusion, and LV systolic dysfunction. HF aetiologies such as ischaemic or non-ischaemic were established using a 12-lead electrocardiogram, echocardiography, and nuclear and/or angiographic examinations by excluding non-cardiac diseases showing similar symptoms and/or signs. Before enrollment to this study, 76 patients had undergone implantable cardioverter defibrillator (ICD) treatment and 56 patients had undergone CRT. Patients with the following diseases or clinical conditions were excluded from this study: positive faecal occult blood, overt gastrointestinal haemorrhage, malignancy, and unstable clinical conditions. Patients who did not provide informed consent on follow-up before discharge were also excluded.

This study included 140 patients (16.8%) with end-stage renal failure who were undergoing haemodialysis. Blood examinations of haemoglobin (Hb), sodium, creatinine, and BNP levels were carried out before discharge. Kidney function was evaluated as estimated glomerular filtration rate (eGFR) using the following formulas: eGFR = 194 × $Cre^{-1.094}$ × $Age^{-0.287}$ for male patients and eGFR = 0.739 × male eGFR for female patients. Plasma BNP level was measured in the initial 367 (44.2%) patients, and N terminal (NT)-pro BNP level was measured in the remaining 462 (56.8%) patients. For the statistical analysis of BNP and NT-pro BNP data, BNP and NT-pro BNP were classified into four stages based on the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF[18]: 0–40 and 0–125 pg/mL for Stage 1; 41–100 and 126–400 pg/mL for Stage 2; 101–200 and 401–900 pg/mL for Stage 3; and 201 and 901 pg/mL for Stage 4.

Two-dimensional echocardiographic examination

Experienced echocardiographers blinded to clinical and nuclear data performed standard two-dimensional echocardiographic study. The following echocardiographic data were measured from apical four-chamber, three-chamber, and two-chamber views in a left lateral decubitus position using commercially available ultrasound machines equipped with a 2.5 MHz variable frequency transducer: left atrium diameter (mm), diastolic left ventricular diameter (mm), diastolic ventricular septal wall thickness (mm), diastolic ventricular posterior wall thickness (mm), LVEF (%), left ventricular end diastolic volume (mL), left ventricular systolic volume (mL), E wave velocity (m/s), LV deceleration time (msec) and septal E/e'. The echocardiographic data used for statistical analysis were obtained in a stable condition prior to discharge.

Assessment of mechanical dyssynchrony and left ventricular mass

Left ventricular mass index and LVMD were evaluated by resting MPI with ^{99m}Tc-tetrofosmin of 300 MBq as shown by our previous study.[4] Briefly, using an electrocardiography-gated approach with a frame rate of 16, a single-head gamma camera equipped with a high-resolution, parallel-hole collimator was used. LVMD was quantified three-dimensionally using all short-axis SPECT images reconstructed with the commercially available gated SPECT software. LVMI was measured by Corridor 4DM version 6.0. LVMD was calculated using Heart Function View (HFV version 1.1)[4] as a standard deviation (SD) of phase angles (degrees) on a phase histogram (*Figure 1*).[8–10] This technique uses mathematical Fourier fitting of myocardial count changes (i.e. time-activity curve) in each pixel during one cardiac cycle, which is basically identical to a regional time-volume curve. Higher ordered Fourier analysis using all time-activity curves over the whole left ventricle enabled calculation of the initiation of systole (regional onset of contraction) as a phase angle. Then a distribution of phase angles three-dimensionally obtained was shown in a phase histogram that provided a phase SD as a parameter of a three-dimensional LVMD (*Figure 1*). This method was confirmed to have high intra-observer and inter-observer reproducibilities evaluated by radiological technicians without having clinical information: CV% of LVMD ranging from 2.93% to 4.56% and CV% of LVMI ranging from 4.42 to 5.86. The correlation coefficients of LVMD and LVMI between operators were $R = 0.994$ ($N = 10$, $P < 0.0001$) and $R = 0.972$ ($N = 10$, $P < 0.0001$), respectively.

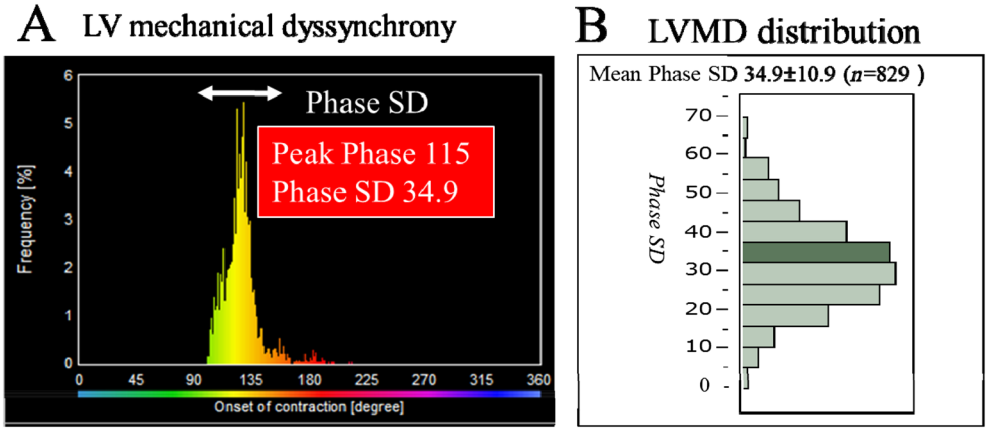
Follow-up protocol

Patients' outcomes were clarified by reviewing medical records. Patients were prospectively and regularly followed up with primary endpoints of the following lethal cardiac events as follows: sudden cardiac death, death due to pump failure, lethal ventricular tachyarrhythmias, and appropriate ICD shock. Sudden cardiac death was defined as witnessed cardiac arrest and death within 1 h after onset of acute symptoms or unexpected death in patients known to have been well within the previous 24 h. This study was based on the principles outlined in the Declaration of Helsinki, and informed consent for enrollment in our database and usage for clinical study was obtained according to the guidelines of the Ethics Committee of our hospital.

Statistical analysis

Basic statistical values are shown as means ± 1 SD. Mean values were compared between the two groups using the unpaired *t*-test. Categorical variables were compared using the χ^2 test. Following univariate analysis, multivariate analysis with a Cox proportional hazard model was performed using the statistically appropriate number of significant ($P < 0.05$) variables identified by univariate analysis, which depended on the number of cardiac events. Hazard ratios and 95% confidence intervals (CIs) were estimated with the use of stratified Cox proportional hazards models. Receiver operating characteristic analysis was performed to determine an optimal cut-off value of an independent significant parameter

Figure 1 Calculation of phase standard deviation (SD) on a histogram (A) derived from gated myocardial perfusion SEPCT imaging. The R-R interval (milliseconds) in each pixel is assigned to 360°, time-activity curves in each pixel are mathematically fitted for the calculation of phase angle, and then a histogram of phase angles three-dimensionally obtained is displayed. The phase angle (degrees) is identical to the onset of contraction, and a wide phase SD indicates greater left ventricular mechanical dyssynchrony (LVMD) of contraction. (B) A histogram of LVMD from 829 patients in this study is shown to approximately have a Gaussian distribution with a mean phase SD of 34.9 degrees.



identified by the Cox multivariate analysis. The Kaplan–Meier method was used to created time-dependent, cumulative event-free curves, which were compared using the log-rank test. For the assessment of incremental prognostic values of significant predictors, global χ^2 values were calculated by combining multivariable predictors, based on increases in the overall likelihood ratio. A computer software programme, SAS for Windows, version 9.4 (SAS Institute, Cary, North Carolina, USA), was used for these analyses. A *P* value less than 0.05 was considered significant.

Results

During a mean follow-up period of 34 months, primary endpoints were documented in 223 patients (27%) as follows: 173 patients (20.9%) died of pump failure, 16 patients (1.9%) had sudden cardiac death, 22 patients (2.7%) had lethal ventricular tachyarrhythmias, and 12 patients (1.4%) experienced appropriate ICD shocks against lethal ventricular arrhythmias. When compared with the non-cardiac event group, patients in the cardiac event group had a more advanced age, greater NYHA functional class, longer QRS duration, lower haemoglobin concentration, and lower kidney function and more frequently had a history of hemodialysis, cardiac device treatment, and/or ventricular arrhythmias (*Table 1*). The cardiac event group more frequently underwent drug treatment using an anti-vasopressin agent and amiodarone. When compared with the non-cardiac event group, the cardiac event group had lower LVEF, greater LV cavity size and left atrial diameter, greater septal E/e', and greater phase SD and LVMI, both of which were assessed by resting ^{99m}Tc MPI (*Table 2*). Receiver operating characteristic analyses showed a phase SD of more than 37 and LVMI of more than 122.7 g/m^2 as optimal cut-off values for the identification of HF patients at a greater risk from others (*Figure 3*). HF patients with phase SD $>$ 37 or LVMI $>$ 122.7g/m^2 had significantly higher cardiac event rate than did other HF patients ($P < 0.0001$) (*Figure 2*). When classified into four patient subgroups using both cut-off values of phase SD and LVMI, HF patients with phase SD $>$ 37 (LVMD) and LVMI $>$ 122.7g/m^2 had the highest cardiac event rate among the patient subgroups ($P<0.0001$).

Among significant univariate variables (*Table 3*), the multivariate Cox proportional hazards model showed that phase

Table 1 Comparison of clinical data and medication between groups with and without cardiac events

	Cardiac events group (n = 223)	Non-cardiac events group (n = 606)	*P* value
Age (years)	70.8 ± 11.3	65.9 ± 12.2	$P < 0.0001$
Gender (male patient/female patient)	163/60	447/159	ns
NYHA (I/II/III/IV)	73/65/74/11	553/43/7/3	$P < 0.0001$
QRS duration (msec)	138.1 ± 36.8	120.8 ± 28.0	$P < 0.0001$
Past history			
Hypertension	113 (50.6%)	316 (52.1%)	ns
Diabetes mellitus	62 (27.8%)	232 (38.1%)	$P = 0.0176$
Dyslipidemia	76 (34.1%)	258 (42.6%)	ns
Atrial fibrillation	80 (35.9%)	155 (25.5%)	ns
Ventriculartachycardia/ventricular fibrillation	58 (26.1%)	76 (12.5%)	$P = 0.0002$
Hemodialysis	54 (24.2%)	86 (14.2%)	$P = 0.0156$
Etiology			
Ischemic	102 (45.7%)	332 (54.7%)	$P = 0.0216$
Prior myocardial infarction	79 (35.4%)	272 (44.8%)	$P = 0.0066$
PCI	76 (34.1%)	258 (42.5%)	$P = 0.0003$
CABG	44 (19.7%)	83 (13.6%)	$P = 0.0505$
Device implantation			
ICD implantation	32 (14.3%)	44 (7.2%)	$P = 0.0026$
CRT implantation	22 (9.8%)	32 (5.3%)	$P = 0.0368$
Laboratory data			
Hemoglobin (g/dL)	11.5 ± 2.1	12.4 ± 2.2	$P < 0.0001$
eGFR (ml/min/1.73 m^2)	33.8 ± 26.3	50.9 ± 26.5	$P < 0.0001$
Sodium (mmol/L)	138.9 ± 4.4	139.8 ± 4.6	$P = 0.0188$
BNP/NTproBNP staging(I/II/III/IV)	7/9/16/191	60/108/104/334	$P < 0.0001$
Medication			
ACE-I/ARBs	138 (61.8%)	363(59.9%)	ns
β-blockers	202 (90.5%)	561 (92.5%)	ns
Amiodarone	90 (40.3%)	115 (18.9%)	$P < 0.0001$
Statins	66 (29.5%)	276 (45.5%)	$P < 0.0001$

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; ns, no significance; NYHA, New York Heart Association Classification. PCI, percutaneous coronary intervention
Values are shown as means ± one standard deviation

Table 2 Comparison of two-dimensional echocardiographic (A) and scintigraphic (B) parameters between groups with and without cardiac events

	Cardiac events group (n = 223)	Non-cardiac events group (n = 606)	P value
(A) Echocardiographic parameters			
M-mode			
LVDd (mm)	56.4 ± 12.1	54.3 ± 8.6	0.0080
LVDs (mm)	47.5 ± 13.1	43.6 ± 9.5	$P < 0.0001$
LAD (mm)	43.3 ± 7.9	40.3 ± 6.9	$P < 0.0001$
IVSTd (mm)	10.3 ± 3.0	10.2 ± 2.5	ns
PTWd (mm)	10.3 ± 2.8	10.2 ± 2.1	ns
Modified Simpson method			
LVEF (%)	33.5 ± 11.4	37.8 ± 8.9	$P < 0.0001$
EDV (ml)	165.0 ± 80.3	147.7 ± 54.1	0.0004
ESV (ml)	115.4 ± 73.7	91.6 ± 46.9	$P < 0.0001$
Doppler method			
E wave velocity (m/sec)	0.86 ± 0.28	0.79 ± 0.28	0.0067
Dct (msec)	184.6 ± 92.9	199.2 ± 76.1	0.0257
Tissue Doppler method			
Septal E/e'	20.1 ± 8.0	16.7 ± 6.9	$P < 0.0001$
(B) Rest ^{99m}Tc-scintigraphic parameters			
Phase SD	37.4 ± 11.5	33.0 ± 10.5	$P < 0.0001$
Left ventricular weight (g)	210.6 ± 54.0	189.5 ± 41.9	$P < 0.0001$
LVMI (g/m^2)	137.4 ± 32.9	115.9 ± 25.5	$P < 0.0001$

Dct, left ventricular deceleration time; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; LAD, left atrial diameter; LVDd, end-systolic left ventricular diameter; LVEF, left ventricular ejection fraction; LVMI, Left ventricular mass index; IVSTd, end-diastolic interventricular septal wall thickness; ns, no significance; PWTd, end-diastolic posterior wall thickness; SD, standard deviation.
Values are shown as means ± one standard deviation.

SD and LVMI were significant independent predictors of cardiac events with hazard ratios of 1.038 (CI, 1.024–1.051, $P < 0.0001$) and 1.005 (CI, 1.001–1.008, $P = 0.0073$), respectively, as well as conventional clinical parameters such as age, NYHA functional class, QRS duration, and eGFR and BNP levels (*Table 3*). Age of more than 74 years, eGFR less than 43 mL/min/1.73m^2, and BNP-NT proBNP Stage 4 were identified as optimal cut-off values for detection of subpopulations at greater risks for lethal events (*Figure 4*). When the clinical parameters were combined with phase SD (LVMD) and LVMI, the prognostic power assessed by the global χ^2 value additionally ($P<0.0001$) increased significantly as follows: 5.9 for age; 139.5 for age and NYHA; 157.9 for age, NYHA, and eGFR; 163.9 for age, NYHA, eGFR, and BNP/NT proBNP stage; 183.4 for age, NYHA, eGFR, BNP/NT proBNP stage, and phase SD (LVMD); and 192.5 for age, NYHA, eGFR, BNP/NT proBNP stage, phase SD (LVMD), and LVMI (*Figure 5*).

Discussion

The results of the present study clearly showed that LVMI and three-dimensional LVMD are independently and synergistically related to lethal cardiac events in combination with conventional HF risks. The results not only indicate diagnostic and prognostic values of the abnormalities for better risk stratification of advanced HF patients but may also therapeutically contribute to better discrimination of appropriate CRT candidates with high-risk LV hypertrophy/LVMD from those without who will have less benefit from CRT.

Three-dimensional left ventricular hypertrophy and mechanical dyssynchrony

Global LVMD was evaluated as an increased SD of phase angles by Fourier fitting and histogram analysis with gated MPI data. Phase SD is a self-standardized parameter of heterogeneity of temporal data (i.e. an onset of systolic phase) without significant artefactual errors when compared with the bandwidth of 95% phase angles on a histogram.[16] Recent advances in computer-assisted analysis of four-dimensional gated MPI data make this method applicable in routine nuclear cardiology practice. Three-dimensional LVMD assessed by gated MPI has several advantages when compared with conventional dyssynchrony assessment using electrocardiography or two-dimensional echocardiography. Gated MPI study can quantify LV dyssynchrony responsible for HF in a three-dimensional manner without any dead angle. Myocardial perfusion abnormality can be evaluated as an aetiology of myocardial injury and LVMD. This is also practically very important for selecting an appropriate pacing site for effective CRT in terms of identification of the regional viable myocardium.[17] The results of this

study showed that the statistical power of QRS is barely significant with a hazard ratio of 1.004 (95% CI, 1.000–1.008) and lower than that of phase SD with a hazard ratio

Figure 2 Determination of optimal cut-off values of phase standard deviation (37) and left ventricular mass index (122.7 g/m^2) for identification of high-risk heart failure patients by ROC analysis. ROC, receiver operating characteristic.

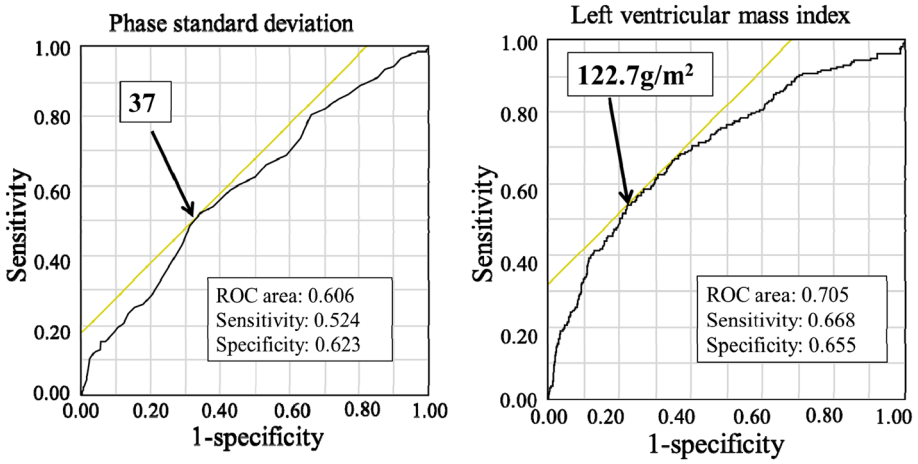


Figure 3 Kaplan–Meier estimates of cardiac event-free survival stratified by phase SD > 37 (A) and LVMI > 122.7g/m^2 (B). When classified using both cut-off values, heart failure patients with the greatest cardiac event rate are identified (C). LVMI, left ventricular mass index; SD, standard deviation.

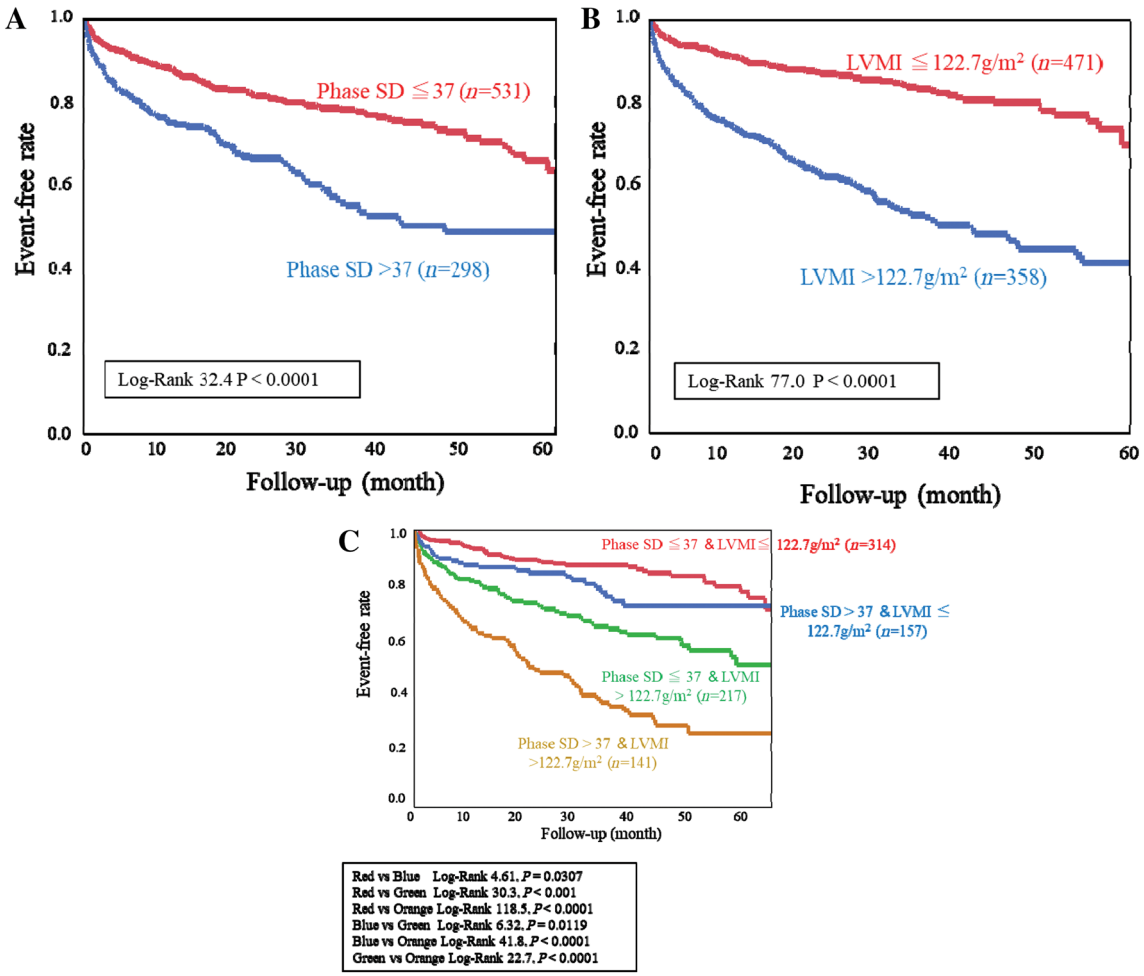
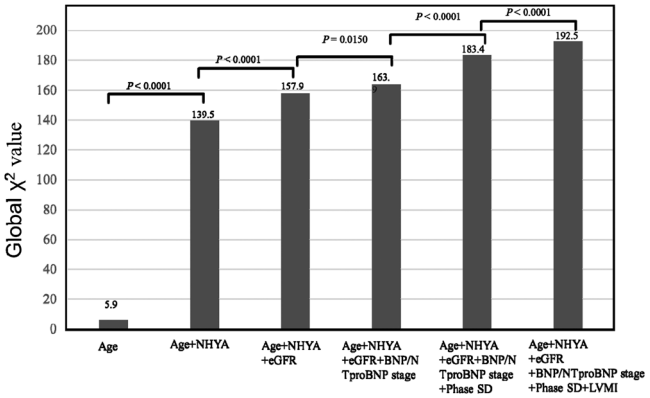
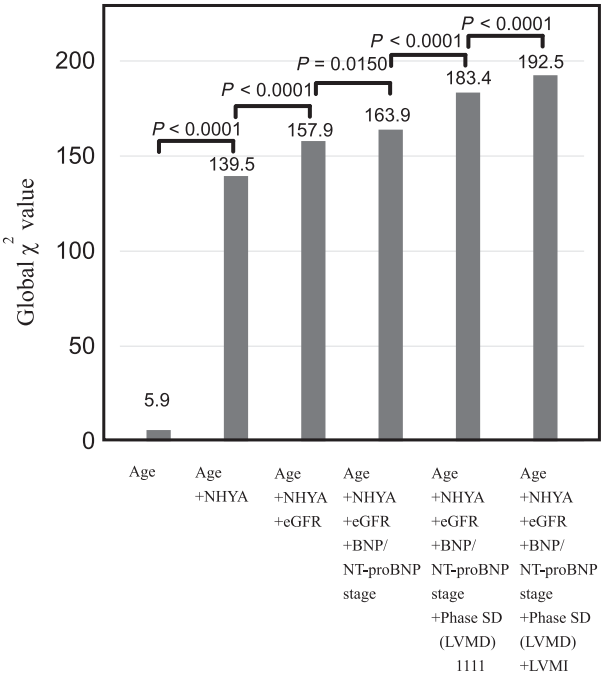


Figure 4 Receiver operating characteristic analysis showed that an age of more than 74 years, estimated glomerular filtration rate (eGFR) less than 43 mL/min/1.73 m^2 and BNP-NT-proBNP Stage 4 or more are optimal cut-off values for discrimination of greater risk populations. LVMI, left ventricular mass index; NT-proBNP, N terminal-pro BNP; NYHA, New York Heart Association; SD, standard deviation.



of 1.039 (95% CI, 1.0024–1.051). From these findings, the three-dimensional mechanical dyssynchrony index, phase SD, is likely to be superior to the QRS duration for prediction of cardiac outcomes in HF patients.

Figure 5 Incremental prognostic powers assessed by global χ^2 values using the six significant multivariate predictors of cardiac events: NYHA functional class, estimated glomerular filtration rate (eGFR), BNP/NT-porBNP, LVMI (>122.7 g/m^2), and phase SD > 37 defined as left ventricular mechanical dyssynchrony (LVMD). LVMI, left ventricular mass index; NT-proBNP, N terminal-pro BNP; NYHA, New York Heart Association; SD, standard deviation.



In addition to conventional analysis of left ventricular function, high-ordered Fourier analysis for calculation of phase SD has a high reproducibility and reliable quantitativity.[18] In contrast, prolongation of QRS complex indicates just an electrical but not mechanical dyssynchrony and is non-specific in terms of HF aetiology, HF condition, and ultimate clinical outcomes.[16] Recent advances in imaging technique such as speckle tracking echocardiography and strain–encoded magnetic resonance imaging are very promising.[19,20] These methods, however, still remain to be investigated clinically in terms of feasibility and reproducibility together with myocardial viability assessment that is necessary for effective CRT and better outcomes.

Conventional clinical biomarkers

Regardless of LV systolic failure, LVMI, NYHA functional class, kidney function (eGFR), and BNP level have been consistently identified as prognostic determinants as shown by the present study and previous studies. In combination with increased LVMI and LVMD, HF patients aged more than 74 years who have a greater NYHA class, eGFR less than 43 mL/min/1.73m^2, and/or BNP-NT-proBNP Stage 4 were identified to be at the greatest risk for lethal cardiac events. These findings strongly suggest that their clinical outcomes can be improved by prevention or amelioration of LV hypertrophy and kidney dysfunction together with treatment of their underlying diseases responsible for these conditions and LVMD. Impaired kidney function or chronic kidney disease and anaemia are known to be closely correlated with cardiac outcomes in HF patients, independently of LV systolic function.[3,4,21,22] The precise mechanisms underlying cardiac mortality have not been determined. Together with the results of our previous studies,[21–24] however, it has been shown that

Table 3 Results of univariate and multivariate analyses

	Univariate analysis					Multivariate Cox hazard model analysis				
			95% CI					95% CI		
	χ^2	Hazard ratio	Lower	Upper	*P* value	χ^2	Hazard ratio	Lower	Upper	*P* value
Age	28.7	1.040	1.020	1.056	<0.0001	25.6	1.040	1.025	1.056	<0.0001
NYHA functional class	258	2.341	2.849	2.750	<0.0001	75.1	2.341	1.991	2.750	<0.0001
VT/Vf	10.6	1.037	1.145	1.666	0.0011	4.50	1.037	1.028	1.666	0.0338
Haemoglobin level	25.2	0.896	0.807	0.972	<0.0001	6.91	0.896	0.827	0.972	0.0086
eGFR	52.6	0.982	0.976	0.988	<0.0001	26.6	0.982	0.974	0.988	<0.0001
BNP/NT-pro BNP stage	57.1	1.451	1.621	1.836	<0.0001	12.6	1.451	1.172	1.836	<0.0001
Amiodarone	43.2	1.832	1.959	2.504	<0.0001	14.0	1.832	1.338	2.504	0.0002
Statin	12.8	0.748	0.452	1.009	0.0005	3.60	0.748	0.549	1.009	0.0575
LAD	49.6	1.018	1.048	1.039	<0.0001	2.86	1.018	0.997	1.039	0.0903
LVEF	41.2	0.975	0.944	0.994	<0.0001	6.22	0.975	0.955	0.994	0.0126
ESV	38.4	1.001	1.004	1.004	<0.0001	0.29	1.001	0.997	1.004	0.5862
Septal E/e'	30.6	1.010	1.032	1.029	<0.0001	1.21	1.010	0.991	1.029	0.2696
Phase SD	33.8	1.038	1.024	1.051	<0.0001	31.5	1.038	1.024	1.051	<0.0001
LVMI	78.3	1.005	1.017	1.008	<0.0001	7.19	1.005	1.001	1.008	0.0073

CI, confidence interval; eFGR, estimated glomerular filtration rate; ESV, left ventricular end-systolic volume; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVMI, Left ventricular mass index; NYHA, New York Heart Association; SD, standard deviation.

impairment of **cardiac sympathetic nerve function may exacerbate** LV hypertrophy and increase LVMD **in association with cardio-renal anaemia syndrome,**[25] leading to lethal **cardiac events in HF patients.**

Clinical implications

Left ventricular hypertrophy and mechanical dyssynchrony is induced and exacerbated three-dimensionally by inhomogeneous contraction abnormalities, in relation not only to an electrical conduction delay but also, sometimes more importantly, to underlying heterogeneous myocyte injury depending on the HF aetiology. The limited prognostic efficacy of CRT in some HF patients strongly suggests the need from clinical and economical points of view to more appropriately identify high-risk HF patients who can respond to CRT. Among several mechanisms involved in each patient, it is technically important to identify sufficiently viable myocardium that is most responsible for increased LVMD and is capable of improving global LV function and ultimate outcomes via an appropriate mechanical resynchronization. LVMI and LVMD can be powerful biomarkers of prognosis, and three-dimensional assessment can contribute to better identification of HF patients who are at increased risk for lethal events and who need more aggressive treatment. Better risk stratification of high-risk HF patients by three-dimensional LVMD assessment may also improve the efficacy and cost-effectiveness of CRT.

Limitations

This study was an observational, single-centre study. A prospective, multi-centre, interventional study is required to clarify the clinical implications of the method presented here and findings. The method possibly contributes to appropriate use of CRT, but it is also necessary to establish a cost-effective therapeutic strategy in high-risk HF patients identified by the method. A future interventional study with CRT is needed to clarify the clinical efficacy of our findings. In addition to unnecessity of a contrast medium or stress agent in this method, it is important to develop a safer protocol with less radiation exposure. Despite the less tracer activity used, recent advances in semiconductor gamma-camera systems have enabled definite reduction in radiation exposure with a sufficient data volume and better spatial resolution.[25,26] By the addition of LVMI and LVMD data to conventional functional and perfusion data, the present method can improve the cost-effectiveness of standard-gated MPI study without additional cost or imaging protocol. The present method may contribute to an overall increase in the cost-effectiveness of CRT and gated MPI by reducing unnecessity CRT or non-responders.

Conclusions

Structural remodelling and systolic mechanical dyssynchrony three-dimensionally assessed are synergistically related to unfavorable cardiac outcomes in combination with conventional clinical parameters such as age, NYHA functional class, kidney function and BNP level. The three-dimensional assessment contributes diagnostically to better risk stratification of high-risk HF patients who need more aggressive treatment and therapeutically to better discrimination of high-risk HF patients who can respond to more aggressive modification of the abnormalities, including device treatment.

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Conflict of interest

None declared.

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