The risk stratification in patients with heart failure: the value of considering both global longitudinal left ventricular strain and mechanical dispersion

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The risk stratification in patients with heart failure: the value of considering both global longitudinal left ventricular strain and mechanical dispersion

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In previous studies mechanical dispersion (MD) predicted ventricular arrhythmias independently of left ventricular ejection fraction (LVEF). Moreover the combination of MD and global longitudinal strain (GLS) increased the prediction of arrhythmic events. We investigated the prognostic value of a new 2D-strain index, GLS/MD, in patients with heart failure (HF). We analysed 340 consecutive HF outpatients in sinus rhythm. Echocardiography was performed at 1.6 ± 0.4 months after hospital discharge. The end point included sudden cardiac death, ventricular fibrillation and sustained ventricular tachycardia (SCD/VA). During the follow-up period (36 ± 9 months) SCD/VA occurred in 48 patients (14.1%). By using the multivariate Cox regression analysis, including LVEF, early diastolic transmitral/mitral annular velocity ratio (E/E'), GLS, MD and GLS/MD in the model, GLS/MD was the best independent predictor of SCD/VA (HR=3.22, 95% confidence interval =1.72-6.15, $p=0.03$). Separate inclusion of LVEF, systolic mitral annular velocity, E/E' , GLS and MD together with GLS/MD, showed that GLS/MD remained the best predictor of SCD/VA (each $p<0.05$). The optimal GLS/MD cut-off value to predict SCA/VA was -0.20 %/ms (80% sensitivity, 76% specificity). Irrespective of LVEF, free survival was significantly better in patients with $GLS/MD \leq -0.2$ %/ms (log-rank, $p<0.001$). In conclusion, GLS/MD may improve cardiovascular risk stratification in subjects with HF.

Keywords: heart failure, malignant ventricular arrhythmia, cardiovascular risk stratification, 2D-strain imaging, global longitudinal strain, mechanical dispersion, GLS/MD ratio

Introduction

Cardiac imaging is indispensable for heart failure (HF) patients' management. Prognosis in cardiac disease is closely related to systolic function which is commonly assessed using left ventricular ejection fraction (LVEF). Two-dimensional strain echocardiography may potentially save additional lives using a more appropriate risk stratification of patients with HF. An increasing number of studies have suggested that LV global longitudinal strain (GLS) is a robust, well validated and reproducible marker for the measurement of LV longitudinal deformation, which is superior to EF, both as a measure of LV function and as well as a predictor of mortality and cardiac events ([Cho et al. 2009](#); [Ersbøll et al. 2013a](#); [Huagaa et al. 2012](#); [Iacoviello et al. 2013](#); [Kalam et al. 2014](#); [Mignot et al. 2010](#); [Russo et al. 2014](#); [Smiseth et al. 2016](#); [Stanton et al. 2009](#)). A cutoff value for GLS as a marker of high mortality risk is not available at the moment ([Smiseth et al. 2016](#)). The lack of standardization across commercially available 2D-strain software makes the evaluation of myocardial strain vendor-dependent ([Russo et al. 2014](#)).

Mechanical dispersion (MD), reflecting contraction heterogeneity, is a novel risk-stratifying parameter derived also from 2D-strain imaging. This parameter proved to be an excellent predictor of arrhythmic events independently of LVEF ([Smiseth et al. 2016](#)). MD is calculated as the standard deviation of contraction duration measured from the electrocardiographic R-wave to peak shortening strain in multiple LV segments ([Huagaa et al. 2013a](#)). Normally, all segments have relatively similar contraction duration and therefore low values for MD. MD can be regarded as the mechanical consequence of electrical alterations and tissue abnormalities ([Huagaa et al. 2010a](#)). MD quantification is an accurate parameter in predicting mortality and ventricular arrhythmias in patients with previous myocardial infarction ([Huagaa et al. 2010b](#), [Huagaa et al. 2013a](#)), non-ischaemic cardiomyopathy ([Huagaa et al. 2012](#)),

HF and cardiac resynchronization therapy (CRT) ([Hasselberg et al. 2016](#)). MD may be used as an additive parameter for risk assessment in these populations.

Recently, Huagaa et al. suggested that a combination of MD and global strain may improve the selection of patients with previous myocardial infarction for implantable cardioverter-defibrillator therapy (ICD) ([Huagaa et al. 2013a](#)). Therefore we proposed a new 2D-strain parameter (GLS/MD) and we tested the hypothesis that it might improve the risk stratification of major ventricular arrhythmic events in patients with HF.

Methods

Patients

Four hundred and sixteen consecutive outpatients (age ≥ 18 years) suffering from chronic HF (both with and without reduced HF) with sinus rhythm and optimal medical treatment were prospectively analyzed. All patients were previously hospitalized in Timisoara Institute of Cardiovascular Diseases for exacerbation of HF symptoms with at least 1 New York Heart Association class deterioration, typical signs of HF and echocardiographic evidence of systolic and/or diastolic LV dysfunction ([McMurray et al. 2012](#)). Patients with non-cardiac disease with a life expectancy < 1 year, inadequate echocardiographic images, significant primary valvular heart disease, acute coronary syndrome in the previous 40 days, coronary artery by-pass graft before echocardiographic examination, congenital heart disease, and patients undergoing ventricular pacing were excluded. The study was conducted in full conformity with the current revision of the Declaration of Helsinki. The study was approved by the local research ethics committee and informed consent was obtained from all individual participants included in the study.

Echocardiography

Echocardiography was performed at >1 month of hospital discharge with an ultrasonographic system (Vivid 9 General Electric, Milwaukee, WI) and analyzed using a commercially available software (EchoPAC; GE Vingmed Ultrasound AS). LVEF was assessed from apical 2- and 4-chamber views using a modified Simpson's rule ([Lang et al. 2006](#)). Left atrial (LA) volume was calculated using the biplane area-length method in the apical four-chamber and apical two-chamber views at ventricular end-systole (maximum LA size) ([Lang et al. 2006](#)). The severity of mitral regurgitation was assessed from the apical views using proximal convergence method; the regurgitant orifice area (ROA) and the regurgitant volume (RV) were determined ([Zoghbi et al. 2003](#)). The peak early diastolic velocity of transmitral flow (E) was measured by pulsed-wave Doppler during end-expiratory apnea. Measurement of systolic pulmonary artery pressure (SPAP) was performed using the maximal regurgitant velocity at the tricuspid valve by continuous wave Doppler. The peak early diastolic (E') and peak systolic velocities (S') were determined at the lateral and septal mitral annulus corners using pulsed wave Tissue Doppler Imaging (TDI) ([Nagueh et al. 2009](#)). The average value of the velocities was used for the analysis and E/E' was calculated.

GLS was determined from apical planes (4-, 3-, and 2-chamber view) using 2D-strain echocardiography. Three cardiac cycles from each view were recorded. Aortic valve closure was identified on continuous-wave Doppler recording through the aortic valve. Peak systolic strain was assessed in all LV segments and the values from each segment were averaged to obtain GLS ([Reisner et al. 2004](#)). If more than 3 of the LV segments were inadequately tracked, the patient was excluded from the final analysis. MD was defined as the standard deviation of time measured from the peak R-wave to peak negative strain in multiple LV segments ([Huagaa et al.](#)

2010a). Segments exhibiting only positive strain values, like dyskinetic segments, as well as segments with strain curves oscillating around the zero line, like akinetic segments, were not included in time measurements (Huagaa et al. 2013a). If 6 or more segments did not have sufficient tracking, the patient was excluded from the analyses. GLS/MD was calculated (Figure 1).

Echocardiographic analyses were performed offline by 2 experienced sonographers (M.C. and C.D.) blinded to clinical data. The inter- and intra-observer variabilities for GLS, MD and GLS/MD were examined. Measurements were performed in a group of 30 randomly selected subjects by one observer two separate times and by two investigators who were unaware of one another's measurements and of the study time point.

Clinical Variables Recorded

The following clinical variables were recorded: age, sex, body mass index, mean arterial pressures, heart rate, etiology of HF, NYHA functional class. Prescription of the main therapeutic classes in HF was also noted.

Clinical Outcome

Patients were followed-up for ≥ 24 months. Documented sustained ventricular tachycardia, ventricular fibrillation, and sudden cardiac death were regarded as the study end-point (SCD/VA). Cardiovascular events were assessed from hospital documentation, information from attending physicians and death certificate. No patient was lost to follow-up.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation for continuous variables and as proportions for categorical variables. Continuous variables were compared between groups using unpaired t test (variables with normal distribution) or Mann-Whitney U test (non-normally distributed variables). Proportions were compared using chi-square test and Fischer's exact test. Univariate Cox proportional hazards analysis was performed to investigate the significance of a number of variables in predicting SCD/VA. Some variables associated with outcome were included into a multivariate Cox regression model to identify independent predictors of SCD/VA. The output of this analysis was expressed as hazard ratio with 95% confidence interval. Cumulative events curves were obtained using the Kaplan-Meier method. Patients who died of non-arrhythmic causes were censored (as non-events) at date of death. A p value <0.05 was considered significant. Receiver-operator characteristic (ROC) curves were plotted to define cut-off values of independent predictors. Intra- and inter-observer variability for GLS, MD and GLS/MD were measured by the intraclass correlation coefficient and by the coefficient of variation (CV) with the root-mean-square method. All analyses were carried out with the SPSS, version 18.0 (SPSS Inc., Chicago, Illinois) statistical software.

Results

Baseline characteristics and arrhythmic events

The current prospectively study included 340 consecutive outpatients (63 ± 12 years; 111 women), previously hospitalized for HF, irrespective of LVEF. The mean LVEF was $42 \pm 13\%$ and the aetiology of HF was represented by coronary artery disease (215 patients), non-ischemic cardiomyopathy (87 patients) and systemic hypertension (38 patients). Table 1 presents the baseline characteristics of the 340 patients included in the study.

During the 36 ± 9 months of follow-up, SCD/VA occurred in 48 patients (14.1%). Of these 48 patients, 2 received appropriate shock therapy for ventricular fibrillation from an ICD implanted for primary prevention, 9 had documented ventricular tachycardia requiring cardioversion and 37 died suddenly. Four of the patients requiring cardioversion died during the same hospitalization.

Echocardiographic parameters as markers of arrhythmic risk

Echocardiography was performed at the moment of inclusion in the study (1.6 ± 0.4 months after hospital discharge). Of the initial 416 patients, 65 were excluded because of suboptimal image quality for speckle-tracking analysis and 11 because of event occurrence before being enrolled in the study. The echocardiographic characteristics of the remaining 340 patients with and without arrhythmic events are presented in Table 2. Eight of the 48 SCD/VA patients subgroup (16.7%) already had an ICD implanted compared to only 27 of 292 (9.3%) in the non-SCD/VA subgroup ($p < 0.001$).

Patients who developed SCD/VA had significantly higher SPAP, larger LA and LV volumes, lower LVEF and S' velocities, and higher values for E/E', MD, GLS and GLS/MD as compared with patients without SCD/VA. In addition, there was no difference regarding the

distribution of ROA and RV. Mean GLS/MD ratio was -0.24 ± 0.31 %/ms in patients who developed SCD/VA and -0.83 ± 0.54 %/ms in the rest ($p < 0.001$).

Table 3 shows the echocardiographic variables that predicted SCD/VA on univariate Cox regression analysis ($p < 0.05$): LA volume, LV end-diastolic volume, LV end-systolic volume, LVEF, SPAP, S', E/E', GLS, MD and GLS/MD. By including LVEF, E/E', GLS, MD and GLS/MD ratio in the model, the multivariate forward Cox regression analysis (Table 3) identified GLS/MD as the best independent predictor of SCD/VA (HR=3.22, 95% confidence interval =1.72-6.15, $p=0.03$), while E/E' ratio also remained a good predictor (HR=1.14, 95% confidence interval=1.08-1.22, $p=0.008$). Including GLS/MD together with E/E', only GLS/MD turned out to be a better predictor (HR=2.4, $p=0.003$) than E/E' (HR=1.12, $p=0.001$). Furthermore, separate inclusion of LVEF, S', GLS and MD (all $p > 0.05$) showed that only GLS/MD predicted SCD/VA (all $p < 0.01$). The additional benefit of GLS/MD to predict SCD/VA is shown in Figure 2. However, the addition of GLS/MD markedly improved the prognostic utility of the model containing LVEF, S', E/E', GLS and MD ($p=0.001$).

Figure 3 shows the ROC curve for GLS/MD to predict SCD/VA. The optimal cut-off value was -0.20 %/ms with 80% sensitivity and 76% specificity. Arrhythmia-free survival was significantly better in those with $\text{GLS/MD} \leq -0.2$ %/ms (log-rank, $p < 0.001$) as shown by the Kaplan–Meier analysis (Figure 4a). The median event-free survival time from the baseline echocardiography was 40.3 months in the group of patients with $\text{GLS/MD} \leq -0.20$ %/ms (193 patients, 56.8%) and 29.8 months in those with $\text{GLS/MD} > -0.20$ %/ms (147 patients, 43.2%).

HF with LVEF $\leq$ 35% versus HF with LVEF $>$ 35%

To investigate the possible impact of LVEF, patients with LVEF $\leq 35\%$ (123 patients, 36.2%) and with LVEF $>35\%$ (217 patients, 63.8%) were analyzed separately. The echocardiographic findings of these patients are presented in Table 4. In both groups, E/E', S', GLS, MD and GLS/MD were more altered in those with SCD/VA. The event-free survival rate was significantly higher in patients with GLS/MD $\leq -0.2\%$ /ms (log-rank, $p < 0.001$) regardless of LVEF ($\leq 35\%$ or $>35\%$), as shown by the Kaplan-Meier plots (Figure 4b and 4c).

Reliability and feasibility

The intra-observer intraclass coefficients for GLS, MD and GLS/MD were 0.93 (CV 2.7%), 0.91 (CV 3.1%), and 0.91 (CV 2.9%), respectively. The inter-observer intraclass coefficients for GLS, MD' and GLS/MD were 0.92 (CV 2.8%), 0.90 (CV 3.1%), and 0.91 (CV 3.1%), respectively.

Discussion

To the best of our knowledge this is the first study investigating the value of a new 2D-strain derived index, GLS/MD, to predict major ventricular arrhythmic events in patients with HF, in sinus rhythm. In our work, GLS/MD ratio was the strongest predictor of SCD/VA when compared to other echocardiographic parameters (LVEF, E/E', S', GLS or MD).

The clinical importance of predicting arrhythmic events in patients with or without LV dysfunction is crucial. Previous studies with echocardiographic imaging have suggested that LVEF (Nikitin et al. 2006), LV volumes indices (Nikitin et al. 2006) and LA size (Lim et al. 2009; Rosca et al. 2011) are good predictors of outcome in the setting of congestive HF.

Currently, LVEF alone is used to assess the risk of ventricular arrhythmia and indication for primary prevention ICD in HF patients (Hasselberg et al. 2016; McMurray et al. 2012). LVEF is an obvious marker of prognosis, with a cut off value $<35\%$ indicating poor prognosis, but there is criticism and debate around it (Buxton et al. 2010; Huagaa et al. 2010a; McMurray et al. 2012). On the other hand, remodeling in smaller regions of the LV may be missed by LVEF (Huagaa et al. 2013a). Moreover, in our study, LVEF, predictor of SCD/VA on univariate analysis, was eliminated on multivariate analysis.

Unlike LV volumes and LVEF, TDI does not require tracing of endocardial contours (Nikitin et al. 2006). The E/E' ratio is an index that reflects accurately the LV filling pressure (Nagueh et al. 2009), and it is a strong predictive factor for survival. Møller et al. (2006) studied a group of patients after first myocardial infarction and reported that E/E' was an independent predictor of all-cause death. Other studies (Almeida et al. 2012; Hirata et al. 2009; Olson et al. 2008) reported that E/E' ratio and S' wave (Nikitin et al. 2006) were strong independent predictors of outcome in populations with HF, while S' was a predictor of cardiac mortality in heterogeneous populations of cardiac patients (Mogelvang et al. 2015; Wang et al. 2003). Changes in E' precede the changes in atrial size and atrial enlargement may be a result of long-standing diastolic changes (Huagaa et al. 2013b). A decreased E' value may reflect regional differences in onset of myocardial relaxation resulting from heterogeneity in contraction duration (Huagaa et al. 2009). E' is associated with an intense energy demanding process, influenced by myocardial ischemia, while S' wave indicates myocardial deterioration with increased LV stiffness and consecutive systolic dysfunction (Mogelvang et al. 2015). Nevertheless, TDI has technological limitations such as angle dependence, signal noise, and measurement variability.

Furthermore, the current study demonstrated that in our group of HF patients, GLS/MD predicts SCD/VA better than S' or E/E' .

Two-dimensional strain is not angle-dependent and GLS has proved to be able to detect early LV systolic dysfunction in a variety of conditions, even when LVEF is still in the normal range (Russo et al. 2014). It is thought that longitudinal contraction is a particular marker of subendocardial function, which may be disproportionately involved in subclinical disease, including hemodynamic overload, subendocardial ischemia, or early myocardial damage at a stage when LVEF is not yet impaired (Ersbøll et al. 2013a; Russo et al. 2014; Stanton et al. 2009). GLS correlates with the infarct size and predicts death and HF after acute myocardial infarction as well as cardiovascular outcome (Ersbøll et al. 2013b). Several studies have examined the prognostic value of GLS in unselected populations (Stanton et al. 2009), in stable chronic HF (Cho et al. 2009; Mignot et al. 2010; Nahum et al. 2010), and recently in patients with chronic ischemic cardiomyopathy (Bertini et al. 2012). In HF patients fulfilling CRT indications, GLS before CRT implantation was an important predictor of survival free from death and heart transplantation (Hasselberg et al. 2016). The geometric alignment of the endocardial longitudinal fibers results in a smaller curvature and thus exposes them to greater detrimental effect of increased LV cavity pressure because of the law of Laplace (Ersbøll et al. 2013a). Our findings are consistent with previous studies showing that GLS can detect subtle myocardial changes of prognostic importance in patients with HF and improve arrhythmic risk stratification.

MD, a new parameter derived from 2D-strain imaging, reflects contraction heterogeneity and was an excellent predictor of arrhythmic events independently of LVEF (Huagaa et al. 2013a). Potential etiologies of MD are electrical alterations, fibrosis or ischemia which may

cause local delays in electromechanical activation. Furthermore, non-uniform loading conditions in a diseased ventricle may impact the timing of peak shortening. Previous works have shown strong evidence that MD predicts ventricular arrhythmia in patients with previous myocardial infarction (Huagaa et al. 2010b; Huagaa et al. 2013a), non-ischaemic cardiomyopathy (Huagaa et al. 2012), and with HF and CRT (Hasselberg et al. 2016). Mismatch between electrical and mechanical systole has previously been suggested as a mechanism for ventricular arrhythmias (ter Bekke and Volders. 2012). MD remained a marker of arrhythmias even when excluding patients with wide QRS intervals (Huagaa et al. 2013a). Our findings are in accordance with the previous work of Ersbøll M et al. (2013b) by analyzing patients with acute myocardial infarction where both GLS and MD were significantly and independently related to ventricular arrhythmic events. In our study, adding MD to a model already including GLS did not significantly improve the risk assessment and MD was a poorer predictor than GLS/MD.

The recent development of 2D-strain imaging has facilitated the assessment of long-axis function, which is sensitive to the preclinical phases of HF, as well as the evaluation of LV synchrony. Ventricular arrhythmias and sudden cardiac death in patients with chronic ischemic HF have been shown to be closely related to the extent of myocardial scarring and scar tissue heterogeneity assessed by cardiac magnetic resonance (Ersbøll et al. 2013). It makes no sense to just look at one of the 2D-strain parameters, since they may all provide different important information. Our finding is that combining the information from GLS and MD provides additional value to established arrhythmic risk factors. The addition of GLS/MD markedly improved the prognostic utility of the model containing LVEF, S', E/E', GLS and MD.

Three-dimensional (3D) strain imaging was developed as a new application that takes advantage of pyramidal and strain data that includes the whole LV and that can improve

information about LV segmental and global deformation by avoiding the loss of speckles encountered in monoplane 2D-strain analysis. 3D-strain imaging offers the advantage of simultaneously measuring longitudinal, radial and circumferential strain values in the whole LV myocardium (Rosa et al. 2016). Area strain, a new parameter that reflects the global function assessment of the endocardial myocardium, is uniquely provided by 3D-strain. It represents the sum of longitudinal and circumferential strain vectors. In addition, 3D-strain has been shown to improve reproducibility and accuracy and may be more useful than 2D techniques. Unfortunately, 3D-strain imaging has a limitation of temporal resolution and a vendor-dependent variability of deformation data. However, it holds great promise as a reliable and feasible tool for evaluating both overall and regional myocardial function (Seo et al. 2014).

CRT has proven to be highly effective for improving symptoms and survival of patients with advanced HF and wide QRS. Multicenter studies suggest that the predictive value of echocardiography was not sufficiently robust to replace routine selection criteria for CRT. The PROSPECT trial analyzing 12 echocardiographic parameters of dyssynchrony found that no single parameter could reliably improve patient selection for CRT; nevertheless, in this trial there was a wide variability in the echocardiographic measures' analysis (Chung et al. 2008). A more recent approach using speckle-tracking echocardiography yielded more accurate quantification of regional wall contraction and therefore generated a great deal of interest about their clinical applications for CRT. Strain imaging can play an important supplementary part in CRT on the basis of a case-by-case clinical decision for challenging cases (Khan et al. 2016). Patients undergoing CRT (with high risk of SCD/VA) were not included in our study group.

HF with LV >35%

The reduction in mortality by CRT in HF is well documented ([McMurray et al. 2012](#)). Currently, EF is used to assess risk of ventricular arrhythmia and indication for primary prevention ICD in HF patients. Although the absolute risk for SCD is highest in patients with significantly reduced LVEF, a significant proportion of SCD events occur in patients with LVEF >35%, which underscores the need for improved risk stratification after myocardial infarction ([Ersbøll et al. 2013b](#)). Despite the small number of events in our study, we found that GLS/MD was a marker of ventricular arrhythmic events in patients with LVEF>35%. These results indicate that GLS/MD may be a more accurate marker to detect small changes in myocardial function, which may be important in arrhythmic risk stratification. [Haugaa et al. \(2013a\)](#) demonstrate that after myocardial infarction, MD predicted arrhythmic events independently of LVEF and was an excellent predictor also in patients with preserved LV function. Also [Ersbøll et al. \(2013a\)](#) showed that GLS provides independent information related to death or HF admissions in patients with LVEF >40% over and above well-established risk factors that carry treatment recommendations in current guidelines. In our study GLS/MD showed an independent significant association with incident ventricular events even among subjects with LVEF>35%, and its prognostic value is important to evaluate patients with arrhythmic risk who do not fulfill current ICD indications. The event-free survival rate was significantly higher in the group of patients with $\text{GLS/MD} \leq -0.20 \text{ \%/ms}$ regardless of LVEF ($\leq 35\%$ or $>35\%$).

Limitations

Our results should be considered in the context of several limitations. The number of patients in this study was relatively small. In our study, 2 independent observers performed strain analyses, with excellent intra- and inter-observer reliability. Unfortunately, 18% of patients were

excluded from the initial study group (65 patients presented suboptimal image quality for speckle-tracking analysis) which is a potential bias. In addition, the study center functioned as a tertiary invasive center and therefore the study population may not reflect a general population of patients with HF. However, we were able to reach several significant observations. Coronary artery disease was highly prevalent in the present series and one cannot rule out the occurrence of ischemic events contributing to the sudden death of the patients. Also, the fact that our study sample was predominantly Caucasian limits the generalizability of our findings. Our study is a single-center study and its reproduction in other centers or by multicenter studies would argue for its validity.

Conclusions

In patients with HF, in sinus rhythm, the novel GLS/MD index is an important independent predictor of malignant ventricular events. GLS/MD may improve cardiovascular risk stratification in subjects with HF, irrespective of LVEF value. GLS/MD ratio may become the optimal method for assessment of SCD/VA risk stratification.

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Conflict of interest: none declared.

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Table 1: Baseline characteristics of the study population.

Variable	Data
Mean age (years)	63±12
Female/male gender <i>n</i> (%)	111 (32.6%) / 229 (67.4%)
Body surface area (m ²)	1.85±0.2
Heart rate (beats/min)	67±13
Mean arterial pressure (mmHg)	106±14
Coronary artery disease, <i>n</i> (%)	215 (63.2)
Non-ischemic cardiomyopathy, <i>n</i> (%)	87 (25.6)
Systemic hypertension, <i>n</i> (%)	38 (11.2)
New York Heart Association class I <i>n</i> (%)	28 (8.2%)
class II <i>n</i> (%)	178 (52.4%)
class III <i>n</i> (%)	117 (34.4%)
class IV <i>n</i> (%)	17 (5.0%)
<i>Medical therapy</i>	
Beta blocker, <i>n</i> (%)	294 (86.5)

ACEI/angiotensin receptor antagonist, <i>n</i> (%)	315 (92.6)
Diuretics, <i>n</i> (%)	274 (77.6)
Aldosterone antagonist, <i>n</i> (%)	259 (76.2)
Digoxin, <i>n</i> (%)	61 (17.9)
Nitrates, <i>n</i> (%)	231 (67.9)
Amiodarone, <i>n</i> (%)	32 (9.4)
Follow-up (months)	36±9

* Data are presented as mean ± SD or absolute values (%);

Note: ACEI, angiotensin converting enzyme inhibitor.

Table 2. Baseline echocardiographic findings in the study group.

Characteristics	Non-arrhythmic events (<i>n</i> = 292)	Arrhythmic events (<i>n</i> = 48)	P value
LV end-diastolic volume (ml)	108±34	131±53	0.03
LV end-systolic volume (ml)	61±25	87±29	0.02
LV ejection fraction (%)	43±12	34±14	0.001
Left atrial volume (ml)	88±40	121±51	0.002
Systolic pulmonary artery pressure (mmHg)	40±13	48±17	0.003
Mitral regurgitant orifice area (mm ²)	27±11	28±8	0.35
Mitral regurgitant volume (ml)	38±17	42±25	0.27
E/E' ratio	11.6±4.4	13.8±6.4	<0.001
S' (cm/s)	7.5±2.9	5.1±2.1	0.001
LV GLS (%)	-18.1±6.5	-11.1±6.5	<0.001
LV MD (ms)	39.7±33.1	72.3±27.6	<0.001
GLS/MD index (%/ms)	-0.83±0.54	-0.24±0.31	<0.001

Note: E, early diastolic transmitral velocity; E', early diastolic mitral annular velocity; GLS, global longitudinal strain; LV, left ventricle; MD, mechanical dispersion; S', systolic mitral annular velocity.

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Table 3. Echocardiographic variables associated with major ventricular arrhythmic events in Cox univariate and multivariate analysis.

Variables	Univariate HR (CI 95%)	P-value	Multivariate HR (CI 95%)	P-value
Left atrial volume	1.01 (1.00-1.02)	0.01		
LV end-diastolic volume	1.03 (1.01 - 1.05)	0.02		
LV end-systolic volume	1.08 (1.02 – 1.13)	0.01		
LVEF	0.94 (0.92-0.97)	<0.001	0.98 (0.95-1.01)	0.23
SPAP	1.03 (1.01-1.05)	0.01		
E/E' ratio	1.21 (1.15-1.27)	<0.001	1.14 (1.08-1.22)	0.008
S' velocity	0.63 (0.52-0.75)	0.001		
GLS	1.16 (1.11-1.22)	<0.001	1.01 (0.93-1.09)	0.91
MD	1.02 (1.01-1.03)	<0.001	1.00 (0.97-1.02)	0.13
GLS/MD	2.59 (1.35-4.95)	<0.001	3.22 (1.72-6.15)	0.03

Note: CI, confidence interval; E, early diastolic transmitral velocity; E', early diastolic mitral annular velocity; GLS, global longitudinal strain; HR, hazard ratio; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; S', systolic mitral annular velocity; SPAP, systolic pulmonary artery pressure.

Table 4. Echocardiographic findings in 217 patients with LVEF >35% and 123 patients with LVEF ≤35%.

Characteristics	Patients without arrhythmic events	Patients with arrhythmic events	<i>P</i> value
<i>Patients with LVEF >35%</i>			
LVEF (%)	48.9±9.5	47±8.1	0.21
E/E' ratio	10.6±4.1	18.8±6.9	0.001
S' (cm/s)	9.3±2.9	7.5±1.9	0.004
LV GLS (%)	-18.8±6.1	-13.7±8.1	0.001
LV MD (ms)	31.2±25.2	63.1±29.2	<0.001
GLS/MD index (%/ms)	-0.99±0.52	-0.37±0.41	<0.001
<i>Patients with LVEF ≤ 35%</i>			
LVEF (%)	29.9±5.2	23.4±6.9	<0.001
E/E' ratio	13.6±4.4	17.1±6.1	0.001
S' (cm/s)	3.78±0.5	2.99±0.3	0.002

LV GLS (%)	-14.2±5.6	-8.9±3.5	<0.001
LV MD (ms)	56.9±39.5	80.2±24.1	0.005
GLS/MD index (%/ms)	-0.43±0.04	-0.11±0.02	<0.001

Note: E, early diastolic transmitral velocity; E', early diastolic mitral annular velocity; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; MD, mechanical dispersion; S', systolic mitral annular velocity.

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Figure captions

Figure 1. Representative example of the calculation of GLS/MD ratio. MD was calculated as the standard deviation of time to peak regional negative strain. GLS/MD was determined ($-19.4\%/39.3\text{ms} = -0.49\ \%/ \text{ms}$).

AVC, aortic valve closure; ANT, anterior; GLS, global longitudinal strain; INF, inferior; LAT, lateral; MD, mechanical dispersion; POST, posterior; SEPT, septal.

Figure 2. The additional benefit of GLS/MD ratio to predict arrhythmic events. The addition of GLS/MD ratio markedly improved the prognostic utility of the model containing LVEF, S' wave, E/E' ratio, GLS and MD ($p = 0.001$).

E, early diastolic transmitral velocity; E', early diastolic mitral annular velocity; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MD, mechanical dispersion; S', systolic mitral annular velocity.

* $p < 0.05$

Figure 3. The receiver-operator characteristic (ROC) curve for GLS/MD ratio to predict major ventricular arrhythmic events.

AUC, area under ROC curve; GLS, global longitudinal strain; MD, mechanical dispersion; 95% CI, 95% confidence interval.

Figure 4. Kaplan-Meier survival curves in the overall population (340 patients) with heart failure (a), in those with left ventricular ejection fraction (LVEF) $\leq 35\%$ (b), and in those with LVEF $> 35\%$ (c), according to GLS/MD ratio below and above $-0.2 \text{ \%/ms}$.

GLS, global longitudinal strain; MD, mechanical dispersion.

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Figure 3. The receiver-operator characteristic (ROC) curve for GLS/MD ratio to predict major ventricular arrhythmic events.

AUC, area under ROC curve; GLS, global longitudinal strain; MD, mechanical dispersion; 95% CI, 95% confidence interval.

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