Combined Global Longitudinal Strain and Intraventricular Mechanical Dyssynchrony Predicts Long-Term Outcome in Patients With Systolic Heart Failure

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Background: Left ventricular (LV) ejection fraction (EF) and QRS duration enable prediction of outcome in patients with systolic heart failure (SHF). We assessed the predictive value of global longitudinal strain (GLS) and mechanical dyssynchrony for prognosis in SHF patients.

Methods and Results: Two-hundred and forty SHF patients with LVEF ≤40% were studied. Global LV function and intraventricular mechanical dyssynchrony were calculated as GLS and SD of the time to peak longitudinal strain (SDε) over 18 LV segments. The added value of GLS and SDε for outcome prediction was assessed using nested Cox models. Sixty-six patients (28%) reached the study endpoint of all-cause mortality/heart transplantation over a median follow-up period of 45 months. Baseline variables associated with adverse outcome were age, glomerular filtration rate, pulmonary artery systolic pressure, diabetes and LV end-systolic volume (model $\chi^2=69.8$). The predictive power of the clinical variables was greater with addition of GLS ($\chi^2=81.1$) or SDε ($\chi^2=102.3$) than with LVEF ($\chi^2=73.9$) or QRS duration ($\chi^2=75.5$; both $P<0.005$). GLS (HR, 1.88; $P=0.03$) and SDε (HR, 1.48; $P=0.04$) were independent predictors after adjustment for the baseline variables. Patients with impaired GLS ($\geq-7.8\%$) and mechanical dyssynchrony (SDε $\geq72$ ms) had poor outcome.

Conclusions: Combined assessment of global LV function and mechanical dyssynchrony using speckle-tracking strain enabled the prediction of long-term outcome in SHF patients. (Circ J 2016; 80: 177 – 185)

Key Words: Echocardiography; Heart failure; Mortality; Speckle tracking

Previous studies have shown that various clinical, electrocardiographic, and echocardiographic parameters can facilitate the prediction of long-term outcome in patients with heart failure (HF). Among these parameters, left ventricular (LV) ejection fraction (EF) and QRS duration are well-established predictors in patients with systolic HF (SHF). LVEF has several technical limitations, however, related to geometry, image quality, and reproducibility. In previous contexts, speckle-tracking strain analysis has emerged as a promising and widely used method for assessing global LV function and the regional timing of myocardial contraction, and is associated with low inter- and intra-observer variability. Many studies have shown that global longitudinal strain (GLS), which is the mean peak longitudinal strain of all the LV segments, is superior to LVEF in the prediction of adverse events in several clinical conditions. Further, intraventricular electrical dyssynchrony, as estimated using QRS duration, may result in uncoordinated LV contraction, which in turn leads to a decline in global LV function. Previous studies have shown that intraventricular dyssynchrony on tissue Doppler velocity has increased prognostic value over QRS duration in patients with SHF. In the present study, we assessed the value of the combination of global LV function and mechanical dyssynchrony, both determined on speckle-tracking longitudinal strain analysis, as a potential independent predictor of outcome in patients with SHF.

Methods

This study is a prospective, single-center, observational study. We enrolled consecutive patients aged 20–85 years who were hospitalized with New York Heart Association function class ≥III and LVEF ≤40%. All patients were admitted to the intensive care unit or ward due to decompensated HF via the emergency department. Those patients with known chronic stable
HF admitted for evaluation of LV assist device or heart transplantation were not enrolled in the study. The other exclusion criteria were the presence of atrial fibrillation, severe valvular disease, cardiac or cerebral ischemic events within the past 3 months, or coexisting malignant disease. In addition, patients with a history of pacemaker implantation or device therapy during the study period were also excluded from the study. The ischemic etiology of HF was defined as the presence of one of the following criteria: (1) ≥75% luminal diameter stenosis of the main epicardial coronary artery; (2) history of myocardial infarction or coronary revascularization; and (3) myocardial ischemia or infarction documented using myocardial perfusion on radionuclide imaging. The patients were stabilized by medication and underwent index echocardiography prior to discharge from hospital. The median interval between admission and echocardiography follow-up is 10 days.

The study endpoint was defined as all-cause death or heart transplantation. The study protocol complied with the Declaration of Helsinki and was approved by the local institutional review board.

**Echocardiography**

The subjects underwent detailed transthoracic echocardiography using a commercially available system (Vivid 7; General Electric Vingmed Ultrasound, Horten, Norway). Left atrial volume (LAV), LV volumes and LVEF were assessed in the apical 2- and 4-chamber views using the modified Simpson’s method. All volume parameters were adjusted for the body

**Figure 1.** Longitudinal strain curves in (A) patients who died and (B) those who survived during the follow-up period. White arrows, peak negative systolic strain. (A) Time interval from peak R on electrocardiography to peak negative systolic strain is shown for the mid-lateral segment (blue curve). Patients who died had a more severely impaired GLS and a more dyssynchronous strain pattern than (B) those who survived. GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; QRS, QRS duration; SDε, SD of the time to peak longitudinal systolic strain.
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Table 1. Clinical and Echocardiographic Characteristics

| Clinical characteristics                        | All patients (n=240) | Survivors (n=174) | Non-survivors/heart transplantation (n=66) | P-value |
|------------------------------------------------|----------------------|-------------------|------------------------------------------|---------|
| Age (years)                                     | 61.5±15.9            | 59.4±15.3         | 66.9±16.4                                | 0.001   |
| Male                                           | 173 (72.1)           | 125 (71.8)        | 48 (72.7)                                | 0.89    |
| Ischemic etiology                              | 120 (50.0)           | 87 (50.0)         | 33 (50.0)                                | 1.00    |
| Hypertension                                   | 127 (52.9)           | 83 (47.7)         | 44 (66.7)                                | 0.008   |
| DM                                             | 81 (33.8)            | 51 (29.3)         | 30 (45.5)                                | 0.025   |
| BMI (kg/m²)                                    | 24.2±3.9             | 24.5±3.8          | 23.3±4.1                                 | 0.05    |
| Heart rate (beats/min)                         | 79.6±15.3            | 79.1±15.8         | 80.6±13.8                                | 0.47    |
| QRS duration (ms)                              | 118.2±32.1           | 113.8±28.2        | 129.7±38.4                               | 0.001   |
| Hemoglobin (g/dl)                              | 12.7±2.3             | 12.9±2.1          | 12.2±2.6                                 | 0.06    |
| Serum sodium (mEq/L)                           | 139.0±3.7            | 139.2±3.6         | 138.5±4.2                                | 0.234   |
| GFR (ml/min/1.73 m²)                           | 61.4±31.7            | 66.9±30.7         | 47.5±30.1                                | <0.001  |
| Medications                                    |                      |                   |                                          |         |
| β-blocker                                      | 185 (77.1)           | 136 (77.2)        | 49 (76.5)                                | 0.84    |
| ACEI or ARB                                    | 202 (84.1)           | 152 (87.4)        | 50 (75.8)                                | 0.03    |
| Spirolactone                                   | 41 (17.1)            | 29 (16.7)         | 12 (18.2)                                | 0.79    |
| Loop-diuretics                                 | 208 (86.7)           | 145 (83.3)        | 63 (95.5)                                | 0.02    |
| Echocardiographic data                         |                      |                   |                                          |         |
| LAV (ml/m²)                                    | 59.4±18.4            | 57.2±17.9         | 65.2±18.8                                | 0.006   |
| LV end-diastolic volume (ml/m²)                | 93.1±34.2            | 89.2±31.9         | 103.2±37.9                               | 0.005   |
| LV end-systolic volume (ml/m²)                 | 67.6±30.4            | 63.5±26.8         | 78.3±36.6                                | 0.001   |
| Mitral E/A                                     | 1.75±1.38            | 1.79±1.45         | 1.67±1.23                                | 0.56    |
| Mitral deceleration time (ms)                  | 172.4±84.4           | 175.8±88.9        | 163.4±70.9                               | 0.32    |
| E/e’                                          | 27.7±14.1            | 26.6±13.5         | 30.4±15.5                                | 0.07    |
| RV fractional area change (%)                 | 33.4±12.8            | 34.1±12.4         | 31.5±13.9                                | 0.42    |
| PASP (mmHg)                                    | 37.8±19.1            | 34.4±16.1         | 47.3±23.3                                | <0.001  |
| LVEF(%)                                       | 29.1±7.9             | 30.1±7.4          | 26.3±8.7                                 | 0.001   |
| GLS (%)                                       | −8.2±2.6             | −8.7±2.6          | −6.8±2.2                                 | <0.001  |
| SD(%)                                         | 78.0±33.7            | 69.9±27.4         | 99.2±39.3                                | <0.001  |

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DM, diabetes mellitus; E/A, ratio of peak early to late diastolic filling velocity; E/e’, mitral early diastolic to early diastolic tissue velocity; GFR, glomerular filtration rate; GLS, global longitudinal strain; LAV, left atrial volume; LBBB, left bundle-branch block; LV, left ventricular; LVEF, LV ejection fraction; PASP, pulmonary artery systolic pressure; RV, right ventricular; SD, SD of the time to peak longitudinal strain.

surface area. Mitral early-diastolic filling velocity (E wave), filling velocity during atrial systole (A wave), early-diastolic myocardial relaxation velocity (e’ wave), and pulmonary artery systolic pressure were measured using conventional or tissue Doppler echocardiography. The e’ velocity was calculated from the average of the lateral and septal values. Measurements were averaged over 3 beats and were made by the same observer, who was blinded to the clinical data.

Two-Dimensional Longitudinal Strain Analysis

Two-dimensional longitudinal strain of the LV was analyzed from the 3 apical views (4-chamber, 2-chamber, and long-axis views) using commercial software (EchoPAC 7.0, General Electric Vingmed Ultrasound). For speckle-tracking analysis, the frame rates of gray-scale images were set between 50 and 80 Hz (61±8 Hz). A single beat was analyzed each time, and values from 3 beats were averaged to obtain each index. From an end-systolic frame, a region of interest was traced along the endocardial border, and the thickness of the region of interest was adjusted to include the maximum wall thickness. The software automatically tracked the image speckle and produced the longitudinal strain curves from the 3 apical views. GLS was calculated as the mean peak longitudinal systolic strain of all the LV segments (Figure 1). For measurements of the time intervals, the peak R wave of the QRS complex was defined as the reference point. SD of the time to peak longitudinal strain over the 18 apical, basal, and mid-LV segments (SDe) obtained from the 3 apical views was computed to derive the intraventricular mechanical dyssynchrony. All measurements were performed by an individual researcher blinded to the other clinical characteristics.

Statistical Analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL, USA), and STATA version 10.1 (StataCorp, College Station, TX, USA). Continuous variables were expressed as mean±SD or as median (IQR). Proportions were compared using chi-squared or Fisher’s exact tests. Correlations between continuous variables were assessed using linear regression. Survival curves were estimated using the Kaplan-Meier method, with log-rank test. Predictive variables for mortality were estimated using the univariate and multivariate Cox proportional hazard models. To test whether prognostic significance of the variables changed over time, the proportional hazards assumption was tested on Cox time-dependent analysis. If the variables violated the assumption (P<0.05), the Cox
model was modified by including the interaction of the variables with time. All continuous variables were assessed per unit SD to enhance the comparison of the variables. Variables with a univariate statistical significance \( P < 0.1 \) were selected for inclusion into the multivariate model as follows. First, significant clinical and echocardiographic variables known prior to global LV function and dyssynchrony measurements were entered into the model. A series of nested models, with the addition of the global LV function (LVEF and GLS) or dyssynchrony parameters (QRS duration and SDe), was established. LVEF was entered into the model as a negative variable to produce a positive HR and thereby enable comparison with GLS. The independence and added value of the global LV function and dyssynchrony parameters over baseline variables were assessed on comparison of the model chi-squared at each step. The added value of LV GLS and SDe to predict long-term outcome over LVEF and QRS duration were assessed by calculating the increment in the Harrell C concordance statistic. Bland-Altman method was used for reproducibility calculation. Intra-observer and inter-observer reproducibility and variability of the GLS and SDe were measured by 2 observers (Y.C., C.W.) for 20 randomly selected patients. Each observer measured GLS and SDe twice, with each assessment measured at 2 separate time periods (1 week apart) in a random manner to avoid any memory of measurement between time points. The observer was allowed to select the best beat for measurement each time. All measurements were made by each observer blinded to previous measurements and to the measurements of the other observer. For all tests, \( P < 0.05 \) was considered statistically significant.

### Results

#### Subjects

GLS and SDe measurements in the 3 apical views were available for 240 (90.9%) of the 264 patients who fulfilled the inclusion and exclusion criteria between 1 August 2007 and 31 July 2010. Patients with more than 1 non-analyzable segment in each apical view on 2-D speckle tracking were excluded from the study. There were 77 patients (64.2%) with ischemic etiology receiving coronary revascularization via either surgery (n=32) or percutaneous intervention (n=45) before index echocardiography in the study. Thirty-one patients (25.8%) had not received revascularization due to infarcted myocardium documented on radionuclide imaging and were free of ischemic symptoms during the follow-up period. Twelve patients (10.0%) with myocardial ischemia did not receive coronary revascularization due to patient refusal or freedom from ischemic symptoms during the study period. The baseline characteristics are summarized in Table 1. Sixty-six endpoints (27.5%) were recorded over a median follow-up of 45 months (IQR, 23–57 months). Thirty-six patients died of pumping failure; 11, of ventricular arrhythmia; 12, of infection; 1, of acute stroke; and 1, of acute myocardial infarction. Five patients received heart transplantation during the study period. We identified 2 patients with specific cardiomyopathies. One had cardiac amyloidosis and the other had hypertrophic cardiomyopathy. The first patient received heart transplantation and the second patient died due to pumping failure. Patients reaching the final endpoint of all-cause death or heart transplantation were older and had a longer QRS duration, lower glomerular filtration rate, higher prevalence of hypertension, diabetes and loop diuretics prescription, and lower prevalence of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) prescription. With respect to the echocardiographic parameters, patients who reached the endpoint had lower LVEF and greater LAV, LV volume, pulmonary artery systolic pressure, GLS, and SDe than those who were free from death or heart transplantation.

#### GLS, SDe, and Cardiac Function

For the subjects as a whole, the average GLS and SDe were \(-8.2\pm2.6\%\) and \(78.0\pm33.7\) ms, respectively. GLS worsened with LV remodeling (LV end-diastolic volume: \( r = 0.38, P < 0.001 \); LV end-systolic volume: \( r = 0.48, P < 0.001 \)) and impaired LVEF (\( r = 0.66, P < 0.001 \); Table S1). More severely impaired GLS was moderately associated with mechanical dyssynchrony (SDe: \( r = 0.46, P < 0.001 \)), and worsening of right ventricular (RV) function (fractional area change: \( r = -0.57, P < 0.001 \)), while GLS was weakly associated with worsening of LV diastolic function (LAV: \( r = 0.29, P < 0.001 \); E/e': \( r = 0.23, P < 0.001 \); mitral deceleration time: \( r = -0.32, P < 0.001 \)). Mechanical dyssynchrony (SDe) correlated moderately with QRS duration (\( r = 0.42, P < 0.001 \)) and correlated weakly with aging (\( r = 0.24, P < 0.001 \)), poor LVEF (\( r = -0.32, P < 0.001 \)) and worsening of LV diastolic function (LAV: \( r = 0.17, P = 0.007 \); E/e': \( r = 0.17, P = 0.002 \)).

#### Predictors of All-Cause Mortality or Heart Transplantation

On univariate analysis with a Cox proportional hazard model, the following factors were associated with mortality or heart transplantation: age, diabetes, glomerular filtration rate, use of ACEI/ARB, LAV, LV end-systolic volume, and pulmonary artery systolic pressure (Table 2). A multivariate Cox regression model including the variables identified as significant on univariate analysis showed that age (hazard ratio [HR], 1.72;
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Figure 2. Model chi-squared and hazard ratios of covariates for the prediction of mortality or heart transplantation after adding the information of (A) left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), (B) QRS duration and SD of the time to peak longitudinal strain (SDε), or (C) GLS and SDε. Baseline model: age, glomerular filtration rate (GFR), pulmonary artery systolic pressure (PASP), diabetes mellitus, and LV end-systolic volume (LVESV).
in Figure 2. The addition of GLS or SD\(_\varepsilon\) to a model including baseline variables plus LVEF or QRS duration produced a significant increase in model chi-squared (both P<0.005). LVEF ceased to be an independent predictor when GLS was included in the model (LVEF: HR, 0.98; 95% CI: 0.64–1.51; GLS: HR, 2.39; 95% CI: 1.32–4.33). QRS duration did not remain as an independent predictor when SD\(_\varepsilon\) was included in the model (QRS duration: HR, 1.03; 95% CI: 0.79–1.35; SD\(_\varepsilon\): HR, 1.70; 95% CI: 1.18–2.46). Notably, GLS (HR, 1.48; 95% CI: 1.02–2.15) and SD\(_\varepsilon\) (HR, 1.88; 95% CI: 1.07–2.15) were both independent predictors even after adjustment for the baseline variables.

Table 3 lists the Harrell C concordance statistics of the baseline characteristics, global LV function and intraventricular dyssynchrony. Both GLS and SD\(_\varepsilon\) had higher concordance statistics than the LVEF and QRS duration, respectively (GLS vs. LVEF, 0.697 vs. 0.617, P=0.023; SD\(_\varepsilon\) vs. QRS, 0.720 vs. 0.618, P=0.020). The model with baseline characteristics plus GLS and SD\(_\varepsilon\) had the highest concordance statistics.

### Kaplan-Meier Curve Analyses

**Figure 3** shows the Kaplan-Meier survival curves of patients classified according to median GLS and SD\(_\varepsilon\): group 1, GLS ≥–7.8% and SD\(_\varepsilon\) <72 ms; group 2, GLS <–7.8% and SD\(_\varepsilon\) ≥72 ms; group 3, GLS ≥–7.8% and SD\(_\varepsilon\) <72 ms; and group 4, GLS ≥–7.8% and SD\(_\varepsilon\) ≥72 ms. Group 4 patients (n=78) constituted a very high-risk group (HR, 8.2; 95% CI: 4.4–15.0, P<0.001), followed by group 2 (n=42; HR, 2.9; 95% CI:

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**Table 3. Discrimination Index Analyses**

| Model                      | C-index | 95% CI |
|----------------------------|---------|--------|
| LVEF                       | 0.617***| 0.545–0.688 |
| GLS                        | 0.697***| 0.636–0.758 |
| QRS duration               | 0.618***| 0.546–0.689 |
| SD\(_\varepsilon\)          | 0.720***| 0.653–0.787 |
| Baseline                   | 0.766***| 0.705–0.827 |
| Baseline+LVEF              | 0.778***| 0.718–0.838 |
| Baseline+GLS               | 0.805***| 0.754–0.857 |
| Baseline+QRS duration      | 0.772***| 0.715–0.829 |
| Baseline+SD\(_\varepsilon\) | 0.803***| 0.751–0.855 |
| Baseline+LVEF+QRS duration| 0.780***| 0.722–0.838 |
| Baseline+GLS+SD\(_\varepsilon\)| 0.819***| 0.769–0.869 |

***P<0.001. Baseline model: age, GFR, PASP, diabetes mellitus, and LV end-systolic volume. Abbreviations as in Tables 1,2.
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ally, mechanical dyssynchrony (SDε) on speckle tracking strain had better predictive power than QRS duration and had significant added prognostic value over the baseline characteristics and GLS. Thus, the combined assessment of GLS and SDε through speckle-tracking strain analysis appeared to be clinically relevant in the risk stratification of adverse outcome in patients with SHF.

LVEF is an important parameter for diagnosing and monitoring HF. Previous studies have shown that serial LVEF measurements in patients with HF yield important prognostic information.2,22–24 The current guidelines also indicate that LVEF <35–40% can be used clinically to define significant LV dysfunction and serve as a cut-off for decision making about medical treatment or intervention.23,25 The assessment of LVEF on 2-D echocardiography, however, has several limitations.7 The measurement of LVEF is based on geometric assumptions of LV volume.8 Poor endocardial visualization or distorted geometry of the LV in cases of advanced HF compromises the precise estimation of global LV function and increases the intra- and inter-observer variability.7 Several studies have demonstrated the superiority of GLS over LVEF in predicting outcome or LV remodeling in patients with acute HF, chronic HF, chronic ischemic cardiomyopathy, or acute myocardial infarction.9,15,16,26 Cumulative data show that compared with LVEF, the assessment of LV mechanics with GLS is more reproducible and feasible, does not rely on geometric

Table 4. High-Risk Subject Characteristics

| Clinical characteristics | Groups 1+2+3 (n=162) | Group 4 (n=78) | P-value |
|--------------------------|----------------------|---------------|---------|
| Age (years)              | 60.8±15.8            | 62.9±16.1     | 0.331   |
| Men                      | 112 (69.1)           | 71 (78.2)     | 0.144   |
| Ischemic etiology        | 83 (51.2)            | 37 (47.4)     | 0.583   |
| Hypertension             | 74 (45.7)            | 53 (67.9)     | 0.001   |
| DM                       | 54 (33.3)            | 27 (34.6)     | 0.844   |
| BMI (kg/m²)              | 24.4±3.9             | 23.7±4.0      | 0.169   |
| Heart rate (beats/min)   | 77.3±15.1            | 84.4±14.9     | <0.001  |
| QRS duration (ms)        | 113.9±30.5           | 129.2±33.6    | <0.001  |
| Hemoglobin (g/dl)        | 12.7±2.4             | 12.8±2.3      | 0.148   |
| Serum sodium (mEq/L)     | 139.2±3.6            | 138.6±4.0     | 0.294   |
| GFR (ml/min/1.73m²)      | 64.6±31.5            | 54.9±31.5     | 0.027   |

Data given as mean±SD or n (%). Group 1, GLS <−7.8% and SDε <72 ms; group 2, GLS <−7.8% and SDε ≥72 ms; group 3, GLS ≥−7.8% and SDε <72 ms; group 4, GLS ≥−7.8% and SDε ≥72 ms. Abbreviations as in Table 1.

Reproducibility

The clinical and echocardiographic characteristics of group 4 patients are summarized in Table 4. Group 4 patients had higher baseline heart rate, longer QRS duration, lower glomerular filtration rate, and higher prevalence of hypertension and loop diuretics prescription. With respect to the echocardiographic parameters, group 4 patients had lower LVEF and RV fractional area change, and greater LAV, LV volume, GLS, and SDε than other patients.

Discussion

This study shows that 2-D speckle-tracking strain analysis provides important prognostic information in patients with SHF. GLS was found to be a strong predictor of mortality in patients with SHF, irrespective of the baseline characteristics, and had prognostic power for those with low LVEF. Additionally, mechanical dyssynchrony (SDε) on speckle tracking strain had better predictive power than QRS duration and had significant added prognostic value over the baseline characteristics and GLS. Thus, the combined assessment of GLS and SDε through speckle-tracking strain analysis appeared to be clinically relevant in the risk stratification of adverse outcome in patients with SHF.

LVEF is an important parameter for diagnosing and monitoring HF. Previous studies have shown that serial LVEF measurements in patients with HF yield important prognostic information.2,22–24 The current guidelines also indicate that LVEF <35–40% can be used clinically to define significant LV dysfunction and serve as a cut-off for decision making about medical treatment or intervention.23,25 The assessment of LVEF on 2-D echocardiography, however, has several limitations.7 The measurement of LVEF is based on geometric assumptions of LV volume.8 Poor endocardial visualization or distorted geometry of the LV in cases of advanced HF compromises the precise estimation of global LV function and increases the intra- and inter-observer variability.7 Several studies have demonstrated the superiority of GLS over LVEF in predicting outcome or LV remodeling in patients with acute HF, chronic HF, chronic ischemic cardiomyopathy, or acute myocardial infarction.9,15,16,26 Cumulative data show that compared with LVEF, the assessment of LV mechanics with GLS is more reproducible and feasible, does not rely on geometric
assumptions, and is independent of LV geometry. Compared with LVEF, which is derived from biplane LV images, the GLS, which is derived from 3 apical views of the LV, may be more accurate in the assessment of global LV function. The prognostic value of prolonged QRS duration as a marker of intraventricular dyssynchrony is well established. QRS duration, however, is an indirect marker of intraventricular dyssynchrony and does not reflect actual uncoordinated myocardial contraction, which is the likely cause of a decline in global LV function. Previous studies have shown that mechanical dyssynchrony derived from tissue Doppler velocity analysis is predictive of adverse events in HF patients, independent of the QRS duration and LVEF.\textsuperscript{18,19,27} Moreover, in this study, we noted that intraventricular dyssynchrony derived from strain analysis has significantly better prognostic power than QRS duration in the prediction of mortality. Many dyssynchrony indices that are derived from tissue Doppler velocity rely on the identification of the peak velocity during ejection, which is often not reliable in patients with SHF. Moreover, it is often difficult to identify accurate and consistent peak velocity in patients with SHF.\textsuperscript{27} Compared with tissue Doppler velocity, speckle-tracking strain analysis provides a more reliable measurement of mechanical dyssynchrony because the strain signal contains fewer peaks and has a higher signal-to-noise ratio than the Doppler signal. The combined assessment of GLS and SDe through speckle-tracking strain analysis is advantageous in practice because the peak strain and the time to peak strain of each LV segment can be obtained simultaneously, and the determination of these parameters using speckle-tracking strain analysis is not time-consuming. GLS and SDe analyses can be completed within 5 min, based on our experience.

In the present study, HF patients with depressed GLS and severe dyssynchrony had an extremely poor outcome. The management of these HF patients with less viable myocardium and extremely dyssynchrony remains challenging in clinical practice. Cardiac resynchronization therapy (CRT) is a well-established treatment for advanced HF with left bundle branch block and QRS duration >130 ms under the current class I guideline, but only 19% of the present patients had left bundle branch block. It is also noted that HF patients with low myocardial reserve have a high propensity to non-response even in the presence of mechanical or electrical dyssynchrony.\textsuperscript{28} Furthermore, a recent randomized and multicenter trial indicated that CRT actually increased mortality in patients with SHF and QRS duration <130 ms.\textsuperscript{29} Therefore, the potential benefit of CRT in the patient group is questionable. Compared with other patient groups, the group 4 patients had higher baseline heart rate. A previous study showed that mechanical dyssynchrony was augmented as heart rate increased.\textsuperscript{30} Other studies indicated that heart rate was a risk factor in chronic HF.\textsuperscript{31,32} Ivabradine, as a selective sinus-node inhibitor, can cause heart rate reduction and improve clinical outcome in SHF patients.\textsuperscript{31,32} There are also studies showing that the severity and prevalence of mechanical dyssynchrony increase with ischemic myocardium and mitral regurgitation.\textsuperscript{33,34} The importance of guideline-directed therapy with titration to maximum tolerated doses of ACEI, ARB and β-blocker, as well as ivabradine, cannot be overemphasized.

\textbf{Study Limitations}

Although the predictive power of GLS and SDe for all-cause mortality remained significant after adjustment for the clinical and echocardiographic measures, other parameters, such as natriuretic peptide level or tissue Doppler velocity-derived mechanical dyssynchrony, could have yielded further prognostic information, but they were not analyzed in the present study. Furthermore, the number of subjects and of cardiac events investigated in this study were insufficient to enable identification of various outcome predictors. We used the 18-segment model rather than the 17-segment model for GLS calculation in order to ensure consistency with the 18-segment model for SDe calculation. The 18-segment model, however, may overrepresent the relative importance of the apex. In the present study, we measured longitudinal strain instead of circumferential or radial strain. This measure was chosen because longitudinal strain has been well validated against LVEF in previous studies.\textsuperscript{10,35,36} It is reproducible and does not significantly add to the time taken to perform an analysis. Further investigation, however, is required to determine whether circumferential or radial strain would yield different results compared with those obtained using longitudinal strain. Twelve patients (10.0%) with myocardial ischemia did not receive coronary revascularization during the study period. Presence of residual ischemia may affect the prognosis in those patients. Additionally, because patients with severe valvular disease, atrial fibrillation, implanted device or HF with preserved EF (HFpEF) were not included, the present results should not be extrapolated to these patients. It would be interesting, however, to know whether the major finding could be applied to patients with HFpEF.

\textbf{Conclusions}

GLS and SDe, assessed using speckle-tracking longitudinal strain, were both important and independent predictors of long-term mortality; the present findings also suggest that these parameters may be better than LVEF and QRS duration for risk stratification in patients with SHF. We believe that the combined assessment of GLS and SDe through speckle-tracking longitudinal strain analysis is clinically feasible and may help to identify high-risk patients.

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Supplementary Files

Supplementary File 1

Table S1. Correlates of GLS and SDe

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