Myocardial strain for heart failure with preserved ejection fraction but without diastolic dysfunction

Jin Joo Park¹, In-Chang Hwang¹, Si-Hyuck Kang¹, Jun-Bean Park², Jae-Hyeong Park³ and Goo-Yeong Cho¹*

¹Cardiovascular Center and Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; ²Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea; and ³Department of Cardiology in Internal Medicine, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Republic of Korea

Abstract

Aims Some patients with apparent heart failure (HF) have an ejection fraction (EF) ≥ 50% and elevated levels of natriuretic peptides (NPs), but no significant diastolic dysfunction. Among these, some may have HF, others may not. Myocardial strain is an excellent prognostic factor.

Methods and results Among 4312 consecutive patients with acute HF from three tertiary hospitals, we included 355 patients with EF of ≥50% and elevated levels of NPs, without significant diastolic dysfunction. Patients were classified as having impaired global longitudinal strain (GLS < 16%) or normal GLS (GLS ≥ 16%). The primary endpoint was 5 year all-cause mortality. The mean age was 70.3 years and 49% were female. Overall, 107 patients (30.1%) died at 5 years. As per the definition, 176 (49.6%) patients had impaired GLS and 179 (50.4%) had normal GLS. Patients with normal GLS had lower 5 year all-cause mortality than those with impaired GLS (P < 0.001). When comparing with the 11 365 age-matched and sex-matched controls, patients with normal GLS had the same long-term survival as the controls (P = 0.834), whereas those with impaired GLS had 48% increased risk of all-cause mortality (hazard ratio, 1.48; 95% confidence interval, 1.17–1.89).

Conclusions Among patients with apparent HF and preserved EF but without diastolic dysfunction, those with impaired GLS may be considered to have HF.

Keywords Heart failure; Preserved ejection fraction; No diastolic dysfunction; Myocardial strain; Invisible HF; All-cause mortality

Introduction

Heart failure with preserved ejection fraction (HFrEF) is a syndrome with heterogenous etiologies and pathophysiology¹; thus, its diagnosis can be challenging even for HF specialists. In contrast to heart failure with reduced EF (HFrEF), where 80–85% of patients die of cardiovascular deaths, many patients with HFrEF die of non-cardiovascular deaths,² indicating the possibility that a significant portion of patients diagnosed with HFrEF may not have HF at all. For the diagnosis of HFrEF, the patient should have symptoms and/or signs of HF, elevated levels of natriuretic peptides (NPs), and objective evidence of cardiac functional and structural dysfunction. The key functional abnormality is diastolic dysfunction.³

There exists a group of patients hospitalized for acute HF, with preserved EF but no significant diastolic dysfunction. According to the contemporary definition of HFrEF, these patients may be classified as not having HFrEF.⁴ Consequently, they would be ‘invisible’ to the physicians.⁵

We recently reported that left ventricular global longitudinal strain (GLS) is a better predictor of clinical outcomes than LVEF.⁶ Herein, we sought to examine whether we can identify HF patients using GLS. Furthermore, we sought to evaluate the prognosis of those.
patients compared with controls who had been discharged alive after being hospitalized in the internal medicine department.

**Methods**

**Patients**

The STRain for Risk Assessment and Therapeutic Strategies in patients with Acute Heart Failure (STRATS-AHF) registry (ClinicalTrials.gov. NCT: 03513653) included 4312 patients, hospitalized for acute HF in 3 tertiary university hospitals between January 2009 and December 2016. In brief, patients with signs or symptoms of HF and either lung congestion or objective findings of LV systolic dysfunction or structural heart disease were eligible for the study. According to the definition of acute HF, which refers to rapid onset or worsening of symptoms and/or signs of HF, we included only patients who were hospitalized for acute decompensation. The patients who presented with acute coronary syndrome were excluded. Echocardiography was performed in 4237 (98%) patients. We measured both LVEF and GLS. For comparison of the outcomes with that in the general population, we created a control group comprising 32-fold age-matched and sex-matched patients who had been discharged after being hospitalized in the internal medicine department, using data from the Korean National Health Insurance Service.

The study protocol was approved by the ethics committee at each hospital. Informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

**Echocardiography and strain analysis**

Patients underwent echocardiography during index admission [median time interval between admission and echocardiography: 1 day; interquartile range (IQR): 0–2 days]. Standard techniques were used in accordance with the American Society of Echocardiography guidelines. Detailed measurement of GLS is provided elsewhere. Echocardiography images in DICOM format with acceptable image quality were uploaded to TomTec software (Image Arena 4.6, Munich, Germany). For strain analysis, endocardial borders were traced on the end-systolic frame in three apical views (4-chamber, 2-chamber, and 3-chamber), with end-systole defined by the QRS complex or as the smallest LV volume during the cardiac cycle. The software tracks speckles along the endocardial border and myocardium throughout the cardiac cycle. Peak longitudinal strain was computed automatically, generating regional data from six segments and an average value for each view. For patients in sinus rhythm, analyses were performed on a single cardiac cycle; for patients in atrial fibrillation, strain values were calculated as the average of three cardiac cycles. All strain measurements were performed by one strain specialist in the core laboratory who was blinded to the patients’ other data. GLS measurement was repeated by the same strain specialist after 3 months or later. To validate the reproducibility an additional strain specialist measured GLS in 20 randomly selected patients. The intra-class coefficients of interobserver and intra-observer variability was 97.0% (P < 0.001) and 99.3% (P < 0.001), respectively.

**Study variables and definitions of diastolic dysfunction**

The four recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are septal e′ < 7 cm/s, average E/e′ ratio >14, left atrial (LA) volume index >34 mL/m², and peak tricuspid regurgitation (TR) velocity >2.8 m/s. LV diastolic dysfunction is present if more than half of the available parameters meets these cutoff values. In case of half of the parameters meets the cutoff values (indeterminate), diastolic dysfunction was assumed to be present when patients had E/A > 2.0 or ≥2 of the three parameters meet the cutoff values (E/e′ ratio, TR velocity, and LA volume index). Patients with and without significant diastolic dysfunction were defined as having HFP EF and suspicious HFrEF, respectively.

In a meta-analysis, the normal GLS value was found to range from −15.9% to −22.1%. The lower limit, corresponding to two-fold standard deviations away from the mean in normal Koreans was 16.7%. Using 16% as cutoff, the patients were classified as having impaired (GLS < 16%) or normal (GLS ≥ 16%) GLS.

The primary outcome was the 5 year all-cause mortality according to GLS. The secondary outcomes included the composite of 5 year all-cause mortality and hospitalization for HF. The vital statuses of all patients were collected from the National Insurance data or National Death Records.

**Statistical analysis**

Data were presented as numbers and frequencies for categorical variables and means ± standard deviations or medians with IQR for continuous variables. For comparison among the groups, the χ² test (or Fisher exact test when any expected count was <5 for a 2 × 2 table) was used for categorical variables, and unpaired Student’s t-test and Mann–Whitney U-test, for continuous variables.

Kaplan–Meier curves were plotted and compared using the log-rank test. A Cox proportional-hazards regression
model was used to determine the effect size of GLS as a predictor of all-cause death. A two-sided P value < 0.05 was considered statistically significant. Statistical tests were performed using SPSS, V.22 (IBM, Armonk, NY).

Results

Baseline characteristics of the study population

Of the 4312 patients in the STRATS-AHF registry, 4239 had undergone baseline echocardiography. We excluded 2904 patients with LVEF < 50% or missing LVEF, 57 patients with BNP < 35 pg/mL or NT-proBNP < 125 pg/mL, and 34 patients without GLS measurement. Of these, 899 (71.5%) had HFrEF who had significant diastolic dysfunction. Finally, 355 (28.5%) had suspicious HFrEF without significant diastolic dysfunction (Figure 1). Suspicious HFrEF patients had lower E/e' (10.1 ± 2.7 vs. 20.9 ± 9.9, P < 0.001) and better outcomes than the HFrEF patients (Figure 2).

Among suspicious HFrEF patients, the mean age was 70.3 years and 49% were female and the mean and median GLS were 15.9 ± 0.2% and 16% [interquartile range (IQR), 13–18.9%], respectively. Per the definition, 176 (49.6%) had impaired and 179 (50.4%) had normal GLS. The baseline characteristics were similar between groups, except patients with impaired GLS had a higher incidence of diabetes mellitus, atrial fibrillation (AF), and advanced New York Heart Association Class. Further, they received more mineralocorticoid receptor antagonists (Table 1).

Clinical outcomes of patients without significant diastolic dysfunction

The median follow-up duration was 37.5 months (IQR, 22.5–59.5 months). Overall, 107 patients (30.1%) died at 5 years, and they had more unfavourable baseline characteristics (e.g. older age and more comorbidities).

Regarding outcomes, suspicious HFrEF patients with normal GLS had lower 5 year all-cause mortality and lower the composite of 5 year all-cause mortality or hospitalization for HF than those with impaired GLS (Figure 3, Supporting Information, Table S1). In addition, suspicious HFrEF patients with impaired GLS had better all-cause mortality and the composite of 5 year all-cause mortality or hospitalization for HF than those with HFrEF (Figure 4). Next, we compared the study population with 32-fold (11 365) age-matched and sex-matched controls. Under stratification by GLS, suspicious HFrEF patients with normal GLS had the same long-term survival as controls [HR, 0.98; 95% confidence interval, 0.73–1.33, P = 0.906], whereas those with impaired GLS had 48% increased risk of all-cause mortality (HR, 1.48; 95% confidence interval, 1.16–1.90; P = 0.002) (Figure 5).

Discussion

This study showed that 28% of patients with acute HF with preserved EF and elevated levels of NPs had no significant diastolic dysfunction. The diagnosis of HF of these patients could not be supported by conventional echocardiography.
and the patients would have been classified as not having HF per contemporary definition of HFpEF.\(^\text{12}\) In addition, the results of the present study confirmed the prognostic value of impaired GLS in HFpEF patient without diastolic dysfunction as detected by conventional resting LV echo-Doppler parameters. When stratifying these patients according to GLS and comparing them to age-matched and sex-matched population who had been discharged alive after being hospitalized in the internal medicine department, patients with impaired GLS had a worse prognosis, whereas those with normal GLS (GLS > 16%) had similar outcomes as the controls. GLS > 16% corresponds to the normal limit in Koreans. Because HF is a disease with poor prognosis, those with impaired GLS are true HF patients, whereas those with normal GLS may not have HF at all. Therefore, myocardial strain may be used to identify ‘invisible’ HF patients.

HFpEF with and without diastolic dysfunction

In this study, most patients (i.e. 72%) had significant diastolic dysfunction. Diastolic dysfunction contributes to elevation of end-diastolic pressure in the cardiac chambers and to congestive symptoms, for example, pulmonary oedema.\(^\text{13}\) Diastolic dysfunction reflects the structural and functional deterioration in HF. Consequently, those with significant diastolic dysfunction had worse outcomes than those without diastolic dysfunction, as shown in this study.

Interestingly, 28% had no significant diastolic dysfunction. As these patients had symptoms and/or signs of HF and elevated levels of NPs, they are ‘apparent’ HF patients. Nonetheless, by strict application of the contemporary definition of HFpEF, these patients may be classified as not having HFpEF. We cautiously postulate that some may have not developed significant diastolic dysfunction yet, whereas others may not have HF at all. One way to discriminate the true HF patients from those without HF may be stratification according to clinical outcomes, because HF is a disease with a high mortality,\(^\text{14}\) and true HF patients would have worse prognosis than the general population.

Finding true, but invisible heart failure patients

HFpEF is a syndrome with heterogenous etiologies and pathophysiology rather than a single disease entity. Its diagnosis can be challenging, even for HF specialists. There have been attempts to develop diagnostic criteria such as H2FPEF score\(^\text{15}\) or the HFA-PEFF score.\(^\text{16}\) Their generalizability and diagnostic performance varied in clinical studies.\(^\text{12}\) In addition, many patients receive ‘intermediate likelihood’, necessitating additional testing for HFpEF diagnosis.

\[\text{Figure 2} \quad \text{Kaplan–Meier estimates of 5 year all-cause mortality and hospitalization for heart failure in patients with preserved EF. Among patients with preserved EF, HFpEF patients with significant diastolic dysfunction had higher all-cause mortality (A) and higher the composite of all-cause mortality or hospitalization for heart failure (B) than the suspicious HFpEF patients without significant diastolic dysfunction. ACM, all-cause mortality; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; CI, confidence interval.}\]

\[\text{Patients with preserved EF}\]

\[\text{HFpEF with and without diastolic dysfunction}\]

\[\text{Finding true, but invisible heart failure patients}\]
Considering the complexity of these scores, the latest HF practice guidelines recommend a simplified pragmatic approach, like that we used in our study. It is less known how these scoring systems will perform in HF patients with preserved EF but without diastolic dysfunction. Because myocardial strain is based on the speckle-tracking method and directly measures the myocardium, it may assess the myocardial function more accurately and be used to identify a group of patients with similar characteristics within this heterogeneous population. We previously showed that patients with similar GLS had similar prognosis regardless of LVEF. We applied the cutoff value of GLS < 16% to define normal GLS and to stratify the patients. GLS < 16% corresponds to the value two standard deviations away from the mean in previous studies and was the median value in our study population. Our principal finding was that suspicious HFpEF patients with impaired GLS had worse prognosis, whereas those with normal GLS had the same prognosis as controls. Considering HF is a disease with worse prognosis, suspicious HFpEF patients with normal GLS may not have HF at all and are falsely classified as having HF, whereas those with impaired GLS are the true invisible HF patients.

Nonetheless, when considering the current guideline, some authors will disagree with our proposed concept and may consider that GLS is not a diagnostic but a prognostic factor and patients with normal GLS are ‘true HF patients with extremely favourable prognosis’. In medicine, a diagnosis is an attempt at classification of an individual’s

### Table 1 Baseline characteristics of the study population according to global longitudinal strain

|                          | Suspicious HFpEF with impaired GLS | Suspicious HFpEF with normal GLS | P-value |
|--------------------------|-----------------------------------|----------------------------------|---------|
| Age (years)              | 70.8 ± 14.4                       | 69.8 ± 13.6                      | 0.508   |
| Men (%)                  | 53.4                              | 44.7                             | 0.100   |
| Body mass index (kg/m²)  | 24.2 ± 4.0                        | 24.2 ± 4.0                       | 0.862   |
| Past medical history     |                                   |                                  |         |
| Hypertension (%)         | 65.3                              | 55.3                             | 0.053   |
| Diabetes mellitus (%)    | 35.2                              | 21.8                             | 0.005   |
| Ischemic heart disease (%) | 26.1                           | 25.1                             | 0.83    |
| Atrial fibrillation (%)  | 46.6                              | 26.3                             | <0.001  |
| NYHA functional class (%) |                                  |                                  | 0.013   |
| I/II                     | 7.4                               | 8.5                              |         |
| III                      | 41.7                              | 56.9                             |         |
| IV                       | 50.9                              | 34.6                             |         |
| Physical exam            |                                   |                                  |         |
| Systolic BP (mmHg)       | 132.1 ± 29.3                      | 127.8 ± 24.6                     | 0.132   |
| Diastolic BP (mmHg)      | 74.9 ± 18.2                       | 71.5 ± 14.4                      | 0.052   |
| Laboratory findings      |                                   |                                  |         |
| Haemoglobin (mg/dL)      | 12.1 ± 2.4                        | 11.4 ± 2.3                       | 0.022   |
| BUN (mg/dL)              | 23.3 ± 13.4                       | 22.5 ± 15.6                      | 0.641   |
| Creatinine (mg/dL)       | 1.4 ± 1.4                         | 1.4 ± 2.7                        | 0.919   |
| BNP (pg/mL)              | 607 (259–1144)                    | 425 (158–850)                    | 0.173a  |
| NT-proBNP (pg/mL)        | 2709 (1118–6111)                  | 2200 (799–6195)                  | 0.328a  |
| Echocardiographic parameters |                                 |                                  |         |
| E-wave (cm/s)            | 0.8 ± 0.3                         | 0.8 ± 0.3                        | 0.924   |
| E/A ratio                | 0.85 ± 0.48                       | 0.97 ± 0.60                      | 0.098   |
| e’ (cm/s)                | 7.7 ± 2.6                         | 7.8 ± 2.5                        | 0.773   |
| DT (ms)                  | 175.0 ± 66.6                      | 203.8 ± 61.4                     | <0.001  |
| E/e’                      | 10.1 ± 2.6                        | 10.1 ± 2.9                       | 0.989   |
| LV EF (%)                | 57.7 ± 5.7                        | 61.7 ± 5.8                       | <0.001  |
| RVSP (mmHg)              | 42.2 ± 74.2                       | 37.3 ± 14.2                      | 0.503   |
| LVMI (g/m²)              | 108.7 ± 37.3                      | 103.8 ± 30.0                     | 0.508   |
| LAVI (ml/m²)             | 46.2 ± 49.0                       | 35.7 ± 27.5                      | 0.031   |
| GLS (%)                  | 12.5 ± 2.7                        | 19.3 ± 2.4                       | <0.001  |
| Medication at discharge  |                                   |                                  |         |
| ACE inhibitor or ARB (%) | 40.7                              | 40.7                             | 0.999   |
| Beta-blocker (%)         | 57.0                              | 54.8                             | 0.683   |
| MRA (%)                  | 47.5                              | 43.1                             | 0.005   |

ACE, angiotensinogen converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; DT, deceleration time; GLS, global longitudinal strain; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide, RVSP: right ventricle systolic pressure; RWT, relative wall thickness.

aP by Mann–Whitney U-test.
Figure 3  Kaplan–Meier estimates of 5 year all-cause mortality and hospitalization for heart failure in patients with suspicious HFrEF without diastolic dysfunction. Among suspicious HFrEF without diastolic dysfunction, those with impaired GLS had higher all-cause mortality (A) and higher the composite of all-cause mortality or hospitalization for heart failure (B). ACM, all-cause mortality; GLS, global longitudinal strain; HFrEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; CI, confidence interval.

**Suspicious HFrEF without diastolic dysfunction**

![Graphs showing Kaplan–Meier estimates of 5 year all-cause mortality and hospitalization for heart failure in patients with suspicious HFrEF without diastolic dysfunction.](image)

- (A) All-cause mortality
  - $P = 0.041$
  - HR 1.49 (1.01-2.20)
  - Survival curves for GLS≥16% and GLS<16% over 5 years.

- (B) ACM + HHF
  - $P = 0.057$
  - HR 1.38 (0.99-1.93)
  - Survival curves for GLS≥16% and GLS<16% over 5 years.

| No. at risk | GLS≥16% | GLS<16% |
|-------------|---------|---------|
| GLS≥16%     | 179     | 149     |
| GLS<16%     | 176     | 141     |

| No. at risk | GLS≥16% | GLS<16% |
|-------------|---------|---------|
| GLS≥16%     | 179     | 143     |
| GLS<16%     | 176     | 138     |

Figure 4  Kaplan–Meier estimates of 5 year all-cause mortality and hospitalization for heart failure in patients with HFrEF and suspicious HFpEF with impaired GLS. The mean GLS was 14.7 ± 4.7% for HFrEF and 12.5 ± 2.7 for suspicious HFpEF with impaired GLS. Suspicious HFrEF patients with impaired GLS had lower all-cause mortality (A) and lower the composite of all-cause mortality or hospitalization for heart failure (B). ACM, all-cause mortality; GLS, global longitudinal strain; HFrEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; CI, confidence interval.

**Patients with preserved EF**

![Graphs showing Kaplan–Meier estimates of 5 year all-cause mortality and hospitalization for heart failure in patients with preserved EF.](image)

- (A) All-cause mortality
  - $P = 0.031$
  - HR 1.34 (1.03-1.74)
  - Survival curves for Susp HFrEF, GLS<16% and HFrEF over 5 years.

- (B) ACM + HHF
  - $P < 0.001$
  - HR 1.53 (1.21-1.93)
  - Survival curves for Susp HFrEF, GLS<16% and HFrEF over 5 years.

| No. at risk | Susp HFrEF, GLS<16% | HFrEF |
|-------------|---------------------|-------|
| HFpEF       | 889                 | 531   |

| No. at risk | Susp HFrEF, GLS<16% | HFrEF |
|-------------|---------------------|-------|
| HFpEF       | 889                 | 573   |
condition into separate and distinct categories that allow medical decisions. Therefore, we believe that the incorporation of GLS into diagnosis of HF may be a new, reasonable approach that should be validated in future studies. It is of note that impaired GLS (≤16%) was considered a minor diagnostic criterion in HFA-PEFF score. Because our study population was limited to those with patients without diastolic dysfunction, the magnitude of impaired GLS might be greater than in HFPEF patients including those with diastolic dysfunction.

One of the intriguing findings is the high presence of AF in suspicious HFpEF patients with normal GLS. The diastole consists of three phases, that is, ventricular filling, diastasis, and atrial filling. Although in patients with AF the atrial kick is absent, adequate cardiac output can be maintained even in these patients because most of the ventricular filling occurs during the early ventricular filling. Therefore, the presence of AF does not necessarily mandate the presence of diastolic dysfunction. Accordingly, most patients with AF do not have HF.

Another intriguing finding is the relatively high proportion of NYHA class III-IV dyspnoea in suspicious patients with normal GLS. Dyspnoea is an important symptom, but a subjective one. It can have cardiogenic and non-cardiogenic aetiologies such lung disease. Because dyspnoea is a chief complaint of HF, many patients with dyspnoea may be falsely diagnosed as having HF.

Limitations of the study

The main limitation of the study is the observational study design. Second, despite applying the latest guideline, the diagnosis of diastolic dysfunction was non-invasive: without invasively measured filling pressures exclusion of HF can be problematic. Third, although there exists a significant inter-vendor difference, the reproducibility of global strain measurements was good and in many cases superior to conventional echocardiographic measurements. Forth, there may be controversy regarding the cutoff for normal GLS. Normal reference ranges for GLS have been determined by meta-analysis of study control groups and healthy volunteers. GLS 16–18% and 18–20% are regarded as ‘borderline’ and ‘normal’, respectively. Because the normal value in Korean was 16%, we believe that GLS of 16% was a reasonable cutoff in this study. Fifth, NP levels can be influenced by obesity, sex, age, renal function, and AF; however, it is the intrinsic limitation that applies to most studies involving NP levels. Sixth, because echocardiography was performed during the admission for acute HF, some of the
parameters may be exaggerated than in stable condition. Eighth, we did not capture the cause of deaths which can be important because up to 30% of HfPEF patients die of non-cardiac deaths. Finally, as we enrolled only Asian patients with acute HF, whether the present study findings can be extrapolated to patients with chronic stable HF or non-Asians is unknown.

Conclusions

Among patients with EF ≥ 50% and elevated levels of NPs, without significant diastolic dysfunction, patients with impaired GLS, but not those with normal GLS, had worse outcome compared with age-matched and sex-matched population without HF. Thus, GLS may be used to identify true HF in these patients. This new concept needs validation in prospective studies before applying in the clinical practice.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Predictors of 5-year composite of all-cause mortality and heart failure hospitalization.

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