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ORIGINAL ARTICLE
Heart Failure

Left Ventricular Longitudinal Myocardial Function of Heart Failure Patients With Transition From Reduced to Preserved Ejection Fraction and of Those With Preserved Ejection Fraction

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Background: Left ventricular (LV) longitudinal myocardial function is associated with the outcomes of heart failure (HF) patients. HF with improved ejection fraction (EF), known as HFimpEF, which is defined as current LVEF >40% but any previously documented LVEF ≤40%, has favorable outcomes compared with HF with preserved EF (HFpEF). However, LV longitudinal myocardial function in patients with previously reduced LVEF (<50%) but improved LVEF to within the normal range (≥50%) (HFnorEF) and its association with cardiovascular events remain unclear.

Methods and Results: We studied 70 patients with HFpEF and 65 with HFnorEF. LV longitudinal myocardial function was assessed as global longitudinal strain (GLS). The primary endpoint was defined as cardiovascular death or HF hospitalization during follow-up of 5.6±3.1 years. The GLS of HFpEF patients was significantly lower than that of HFnorEF patients (13.6±3.5% vs. 14.8±2.2%, P=0.02) even when the LVEF was similar. Multivariate Cox proportional hazards analysis showed that GLS was independently associated with cardiovascular events. Furthermore, of the entire study population, patients with GLS >15.0% had fewer cardiovascular events than those without (log-rank P=0.014) among all the patients.

Conclusions: LV longitudinal myocardial dysfunction was more frequently observed in patients with HFpEF than in those with HFnorEF, even when LVEF was similar, and was independently associated with cardiovascular events for HF patients with current LVEF ≥50%.

Key Words: Echocardiography; Global longitudinal strain; Heart failure; Left ventricular ejection fraction

Left ventricular (LV) longitudinal myocardial function is a sensitive marker of subtle abnormalities of LV myocardial performance, and useful for the prediction of outcomes for various type of cardiac diseases at each heart failure (HF) stage, and superior to conventional echocardiographic indices such as LV ejection fraction (LVEF).[1–5] Specifically, LV longitudinal myocardial dysfunction is considered the first marker of a preclinical form of HF with preserved ejection fraction (HFpEF), which is strongly associated with poor outcomes.[1–5] It is well known that nearly half of symptomatic HF patients have normal or preserved LVEF, a patient population that includes patients with current LVEF ≥50% but some previously documented reduced LVEF (rEF) <50%, as well as those with HFpEF. Furthermore, the number of patients with current LVEF ≥50% but previously detected HFrEF may become higher due to current guideline-directed medical therapy with 4 new types of medication. The 2022 America Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) Guideline highlights the importance of the trajectory of LVEF,[6] and that a significant reduction in LVEF over time

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Table 1. Baseline Characteristics of Patients

Variables	Patients with HFnorEF (n=65)	Patients with HFpEF (n=70)	P value
Clinical characteristics			
Age, years	61.0±14.3	69.8±13.9	<0.01
Sex (female), n (%)	25 (39.3)	22 (31.5)	0.40
BMI, kg/m^2	23.1±4.04	22.5±3.57	0.33
Systolic blood pressure, mmHg	129±24.5	130±18.7	0.65
Heart rate, beats/min	72.2±16.5	69.4±14.3	0.29
Ischemic etiology, n (%)	15 (22.7)	16 (22.9)	0.77
NYHA functional class, n (%)			
I	10 (15.4)	14 (20.0)	0.51
II	39 (60.0)	34 (48.6)	0.22
III	14 (21.5)	17 (24.3)	0.84
IV	2 (3.1)	5 (7.1)	0.44
Hematology			
Hemoglobin, mg/dL	13.5±2.3	12.7±2.3	0.049
Serum creatinine, mg/dL	1.28±1.64	1.04±0.85	0.27
eGFR, mL/min/1.73 m^2	60.3±29.1	61.7±18.9	0.73
BNP, pg/dL	62.2 (32.2–116.8)	237 (174.7–379.8)	<0.01
Comorbidities, n (%)			
Hypertension	34 (52.2)	33 (47.1)	0.35
Diabetes mellitus	19 (28.8)	17 (24,2)	0.44
Dyslipidemia	27 (41.0)	24 (34.3)	0.55
Atrial fibrillation	3 (4.5)	10 (14.2)	0.054
Mediations, n (%)			
ACE inhibitor/ARB	43 (65.2)	32 (45.8)	0.04
Sacubitril/Valsartan	9 (13.7)	3 (4.3)	0.07
β-blocker	45 (68.2)	44 (62.9)	0.36
MRA	28 (42.4)	16 (22.9)	0.02
SGLT2i	14 (21.2)	9 (12.9)	0.26
Diuretic	31 (47.0)	25 (35.7)	0.20
Echocardiographic parameters			
LV end-diastolic volume, mL	97.7±34.0	88.4±35.6	0.12
LV end-systolic volume, mL	42.3±17.2	39.6±17.0	0.37
LVEF, %	57.0±4.6	55.7±3.3	0.07
LAVI, mL/m^2	42.9±30.3	51.8±19.4	0.04
LV mass index, g/m^2	117±45.8	138±44.3	0.01
E/e´	15.2±8.3	13.1±6.0	0.10
GLS	14.8±2.2	13.6±3.5	0.02

Data are mean±SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; E/e´, ratio of early transmitral flow velocity to early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HF, heart failure; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonists; NYHA, New York Heart Association; SGLT2i, Sodium-glucose cotransporter 2 inhibitor.

is a prognosticator of poor outcomes, whereas a significant improvement in LVEF over time indicates favorable outcome.[7] The AHA/ACC/HFSA Guideline established a classification of patients with HF with improved EF (HFimpEF), defined as currently showing LVEF >40% but with some previously documented LVEF ≤40%. It has been reported that this patient population is characterized by favorable outcomes compared with those with HFpEF.[8] However, it remains unclear how outcomes for patients with HFpEF compare with those for patients with previously reduced LVEF (<50%) that has improved to the normal range (≥50%). Furthermore, it remains unclear how the LV longitudinal myocardial function of these 2 groups compares and the association with cardiovascular events.

The purpose of this study was therefore to compare the LV longitudinal myocardial function of patients with HFpEF with that of patients with previously reduced LVEF that improved to the normal range (HFnorEF), and to investigate whether LV longitudinal myocardial function is associated with cardiovascular events.

Methods

Study Population

We retrospectively studied 70 patients with HFpEF and 65 patients with HFnorEF at Kobe University Hospital

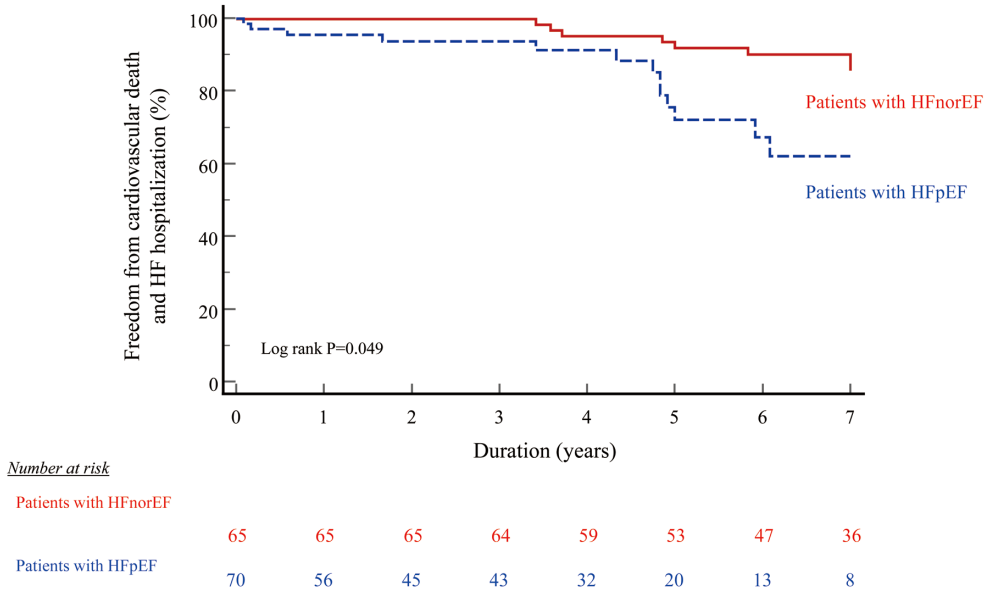

Figure 1. Kaplan-Meier curves of the primary endpoint, showing that patients with HFnorEF had fewer cardiovascular deaths and fewer HF hospitalizations than did those with HFpEF. HFnorEF, heart failure with previously reduced left ventricular ejection fraction (LVEF <50%) but improved LVEF to within the normal range (≥50%); HFpEF, heart failure with preserved ejection fraction.

between January 2014 and October 2022. HFpEF was defined as current and all previous cases of patients with LVEF reported as ≥50% and meeting the HFA-PEFF diagnostic algorithm criteria.[9] HFnorEF was defined as LVEF currently ≥50% but with previously documented LVEF <50% (mean LVEF: 37±10%, 40%≤LVEF<50%: 29 patients; 30%≤LVEF<40%: 16 patients; LVEF <30%: 20 patients). This study was approved by the hospital's Local Ethics Committee in conformity with the Declaration of Helsinki (No. B230030).

Echocardiographic Examinations

Echocardiographic examinations using commercially available echocardiography systems were performed for all patients. Standard echocardiographic examinations were performed in accordance with the current guidelines of the American Society of Echocardiography.[10] Two-dimensional speckle-tracking strain analysis was performed for each patient using dedicated software (AutoSTRAIN, TOMTEC-ARENA; TOMTEC Imaging Systems, Munich, Germany) to evaluate LV longitudinal myocardial function, which was assessed in terms of global longitudinal strain (GLS). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine-formatted file images, were uploaded to a personal computer for subsequent offline GLS analysis, and expressed as an absolute value in accordance with current guidelines.[10]

Definition of Primary Endpoint

The primary endpoint was defined as a composite of cardiovascular death or HF hospitalization for HF over a median follow-up period of 5.6±3.1 years.

Statistical Analysis

Continuous variables are expressed as mean values with standard deviation for normally distributed data and median values with an interquartile range for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. The parameters of 2 groups were compared using Student's t-test or the Mann-Whitney U test as appropriate. Proportional differences were evaluated using Fisher's exact test. Survival curves of freedom from cardiovascular death or HF hospitalization were determined with the Kaplan-Meier method, and cumulative event rates were compared by log-rank test. The initial Cox proportional-hazards analysis to identify univariate associated parameters with cardiovascular death or HF hospitalization was followed by a multivariate Cox proportional-hazards model using the enter method. Moreover, the receiver operating characteristic (ROC) curve was computed to determine the optimal GLS cutoff value for its association with the primary endpoint. For all steps, $P<0.05$ was considered statistically significant. All analyses were performed using commercially available software (MedCalc software version 20.106; MedCalc Software, Mariakerke, Belgium).

Results

Patients' Baseline Characteristics

The baseline clinical and echocardiographic characteristics of the 70 patients with HFpEF and 65 with HFnorEF are summarized in **Table 1**. Patients with HFpEF were significantly older, had lower hemoglobin and higher B-type natriuretic peptide levels, and lower usage of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, larger left atrial volume index, and LV mass index compared with the HFnorEF patients. It was noteworthy that the GLS for patients with HFpEF was significantly lower than that for patients with HFnorEF (13.6±3.5% vs.

Table 2. Univariate and Multivariate Cox Proportional Hazards Analyses

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.034	1.002–1.068	0.038			
Female	2.257	1.063–4.792	0.034	2.481	1.064–5.801	0.035
BMI	0.937	0.847–1.048	0.249			
Hypertension	1.002	0.474– 2.118	0.996			
Diabetes mellitus	0.955	0.405–2.348	0.954			
Atrial fibrillation	0.559	0.075–4.150	0.569			
LAVI	1.010	1.001–1.019	0.025			
GLS	0.787	0.664–0.933	0.006	0.813	0.665–0.990	0.040
BNP	1.001	0.999–1.001	0.168			

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

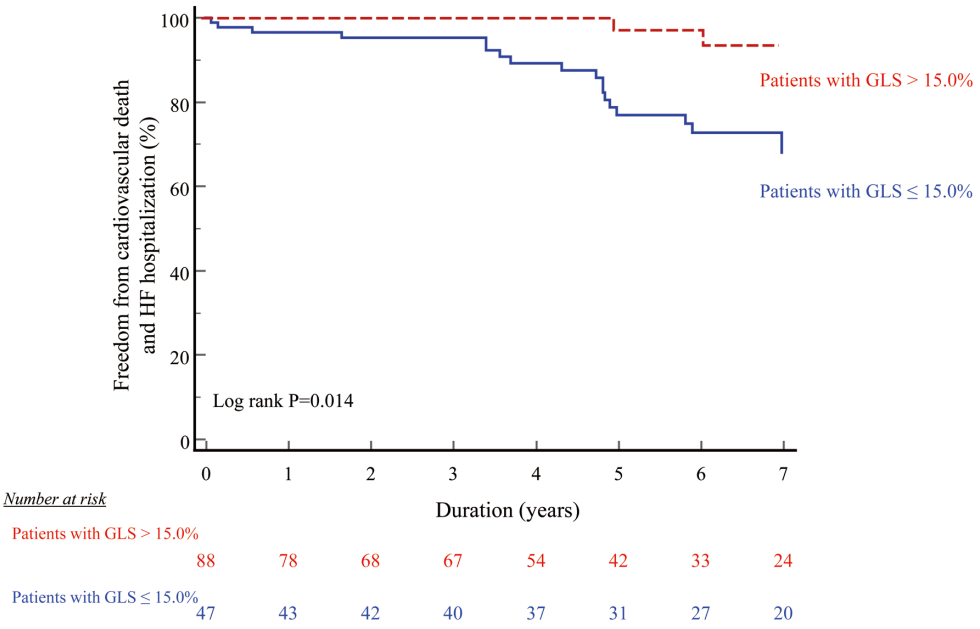

Figure 2. Kaplan-Meier curves of the primary endpoint, showing that, for the entire study population, patients with GLS >15.0% had fewer cardiovascular deaths and fewer heart failure (HF) hospitalizations than those with GLS ≤15.0%. GLS, global longitudinal strain.

14.8±2.2%, P=0.02) even when the LVEF was similar (55.7±3.3% vs. 57.0±4.6%, P=0.07).

Primary Endpoint

The primary endpoint of cardiovascular death or HF hospitalization was recorded for 22 patients (20.7%) during the follow-up period of 5.6±3.1 years. As expected, the Kaplan-Meier curve indicated that patients with HFnorEF experienced significantly better cardiovascular outcomes than those with HFpEF (log-rank P=0.049; **Figure 1**). The hazard ratios and 95% confidence intervals (CIs) for each of the variables of the univariate and multivariate Cox proportional hazards analyses are listed in **Table 2**. An important finding of the multivariate Cox proportional hazards analysis was that GLS proved to be independently associated with cardiovascular death and HF hospitalization (hazard ratio: 0.813, 95% CI: 0.665–0.990, P=0.040). In addition, the ROC curve analysis identified GLS >15.0% as the optimal cutoff value for association with cardiovascular death or HF hospitalization, with a sensitivity of 96%, specificity of 39%, and area under the curve of 0.643 (95% CI: 0.556-0.723; P=0.003). At this cutoff value, the Kaplan-Meier curve indicated that all patients with GLS >15.0% experienced significantly better cardiovascular outcomes than those with GLS ≤15.0% (log-rank P=0.014; **Figure 2**). Next, this cutoff value was applied to each patient group (**Figure 3**). Patients with HFnorEF and GLS >15.0% experienced significantly better cardiovascular outcomes than those with HFnorEF and GLS ≤15.0% (log-rank P=0.045), and patients with HFnorEF and GLS >15.0% tended to have better cardiovascular outcomes than those with HFpEF and GLS ≤15.0% (log-rank P=0.106).

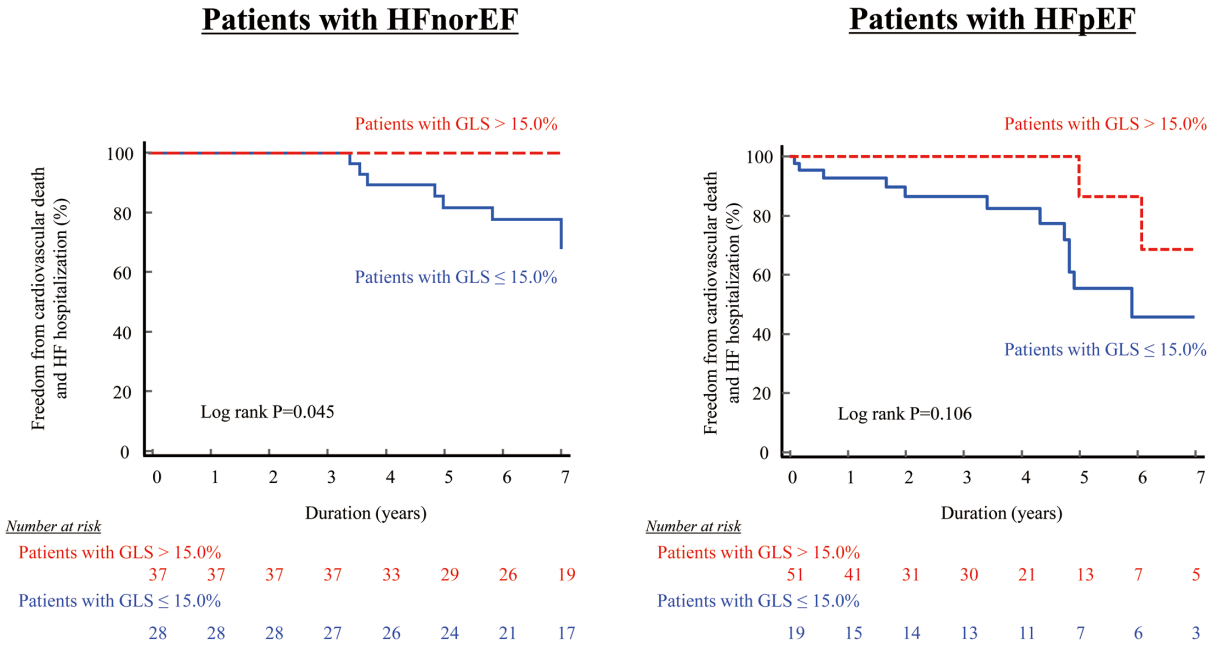

Figure 3. Kaplan-Meier curves of the primary endpoint, showing that patients with HFnorEF and GLS >15.0% experienced significantly better cardiovascular outcomes than those with HFnorEF and GLS ≤15.0%, and patients with HFnorEF and GLS >15.0% tended to be better cardiovascular outcome than those with HFpEF and GLS ≤15.0%. GLS, global longitudinal strain; HFnorEF, heart failure with previously reduced left ventricular ejection fraction (LVEF <50%) but improved LVEF to within the normal range (≥50%); HFpEF, heart failure with preserved ejection fraction.

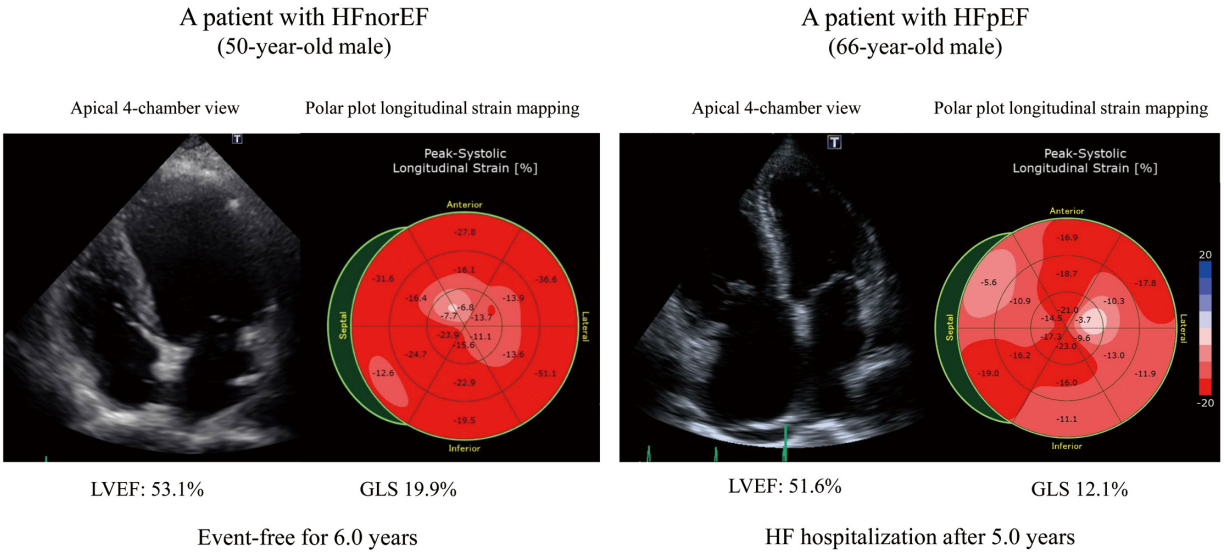

Figure 4. Representative cases of apical 4-chamber view and polar plot longitudinal strain mapping for patients with HFnorEF and HFpEF. GLS, global longitudinal strain; HFnorEF, heart failure with previously reduced left ventricular ejection fraction (LVEF <50%) but improved LVEF to within the normal range (≥50%); HFpEF, heart failure with preserved ejection fraction.

Figure 4 shows representative cases of GLS in a bull's eye plot of patients with HFpEF and HFnorEF.

Discussion

The patients with HFnorEF enrolled in our study had fewer cardiovascular deaths and less frequent HF hospitalization than those with HFpEF. In addition, the GLS for patients with HFpEF was significantly lower than that for patients with HFnorEF, even when LVEF was similar, and the multivariate Cox proportional hazards analysis showed that GLS was independently associated with cardiovascular death or HF hospitalization.

LV Longitudinal Myocardial Function for HF Patients

LVEF is considered important for the classification of HF patients because of differences in prognosis and response to treatments, and because most clinical trials select patients based on LVEF, so a baseline LVEF assessment is mandatory for every HF patient. HF has traditionally been divided into 3 distinct phenotypes based on LVEF measurement: HFrEF, HFpEF, and HF with mildly reduced EF. However, LVEF is not a static measurement and may increase or decrease over time.[11–13] Specifically, LVEF may improve over time during treatment or follow-up for some HF patients with initially low LVEF, so this group has currently received particular attention. Kalogeropoulos et al reported that of 2,166 HF patients, those with increased LVEF during follow-up, which was defined as current LVEF ≥40% but with some previously documented reduced LVEF <40%, registered fewer all-cause deaths, death or all-cause hospitalization, death or cardiovascular hospitalization, and death or HF and needed fewer hospitalizations than did those with HFpEF.[8] Thus, the 2022 AHA/ACC/HFSA Guideline includes a new classification of HF in terms of LVEF, "HFimpEF", which is defined as current LVEF ≥40% but some previously documented LVEF <40%.[6] However, the results of a comparison of outcomes between patients with HFpEF and those with previously reduced LVEF (<50%) whose LVEF had improved to normal range (≥50%) is unclear. Furthermore, the number of patients with current LVEF ≥50% but previously HFrEF with cardiac geometry similar to that of HFpEF but not exactly the same, may be increasing due to the administration of current standard guideline-directed medical therapy with 4 new types of medication for patients with HFrEF, comprising β-blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid-receptor antagonists, and sodium-glucose cotransporter-2 inhibitors (SGLT2i).

GLS as assessed by speckle-tracking echocardiography has been reported to be a sensitive marker of early, subtle abnormalities of LV myocardial performance, helpful for the prediction of outcomes for various cardiac diseases, and superior to conventional echocardiographic indices including LVEF.[1–3] Thus, GLS is currently thought to reflect intrinsic LV myocardial contractility. Moreover, LVEF is not prognostically useful for patients with HFpEF, including those with HFnorEF, which is currently the predominant form of HF.

Clinical Implications

It has recently been reported that nearly half (and possibly more than half) of symptomatic HF patients have current LVEF ≥50%, which includes both patients with pure HFpEF and those with current LVEF ≥50% but some previously documented reduced LVEF <50%. In addition, guideline-directed medical therapy for symptomatic patients with HFrEF now includes 4 types of medication as described above.[6] The LVEF of patients with HFrEF can improve as a result of administration of current guideline-directed medical therapy that includes the 4 new types of medication. It can thus be expected that the number of patients with current LVEF ≥50% but who previously were HFrEF will be increasing. In our study, there were fewer cardiovascular deaths of patients with HFnorEF than of those with HFpEF, and the GLS in patients with HFpEF was significantly lower than that in patients with HFnorEF even when LVEF was similar. Moreover, our multivariate Cox proportional hazards analysis demonstrated that GLS was independently associated with cardiovascular death. Therefore, GLS made risk stratification possible for patients with HFpEF and those with previously reduced LVEF whose LVEF had improved to the normal range even when both patient groups had similar LVEF. According to the 2023 Focused Update of the 2021 European Society of Cardiology Guideline, an SGLT2i, including dapagliflozin or empagliflozin, is recommended as Class I and Level of Evidence A for patients with HFpEF and HF with mildly reduced EF for reducing HF hospitalizations and cardiovascular death.[14] We previously reported that SGLT2i therapy is associated with improvement of GLS, which led to further improvement of LV diastolic function for type 2 diabetes mellitus patients with stable HF (mean LVEF: 62.3%).[15] Thus, GLS-guided management of HF patients with current LVEF ≥50% may be useful for detecting high-risk patients who require close follow-up.

Study Limitations

This study involved a small number of patients in a single-center retrospective study, so future prospective studies with larger patient populations from several centers will be needed to validate our findings. Moreover, an evaluation of quality of life for HF patients, such as the Kansas City Cardiomyopathy Questionnaire score, was not part of this study.

Conclusions

Impaired LV longitudinal myocardial function was more frequently observed in patients with HFpEF than in those with HFnorEF even when LVEF was similar. Moreover, LV longitudinal myocardial function was shown to be independently associated with cardiovascular death and HF hospitalization for HF patients with current LVEF ≥50%. It is hoped that our findings may provide new insights for the management of HF patients.

Disclosures

H.T. has received remuneration from AstraZeneca plc, Otsuka Pharmaceutical Company, Limited, Ono Pharmaceutical Company, Limited, Pfizer Inc., Daiichi Sankyo Company, Limited, and Novartis International AG.

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The remaining authors have no conflicts of interest to declare.

IRB Information

Kobe University Hospital Clinical & Translational Research Center (Reference number: No. B230030).

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