Impacts of Predischarge Diastolic Functional Recovery on Clinical Outcomes in Patients With Hypertensive Heart Failure

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Background: Diastolic function is an independent predictor of death in heart failure (HF), but the effect of a change in diastolic function during hospitalization on clinical outcomes in patients with hypertensive HF (HHF) has been poorly studied. Therefore, the aim of this study was to investigate the effect of predischarge diastolic functional recovery (DFR) on future clinical outcomes in hospitalized patients with a first diagnosis of HHF.

Methods and Results: A total of 175 hospitalized patients with HHF were divided into 2 groups according to the change in diastolic function on predischarge echocardiography in comparison with baseline echocardiography: DFR group (n=74, 54.2±17.1 years, 55 males) vs. no DFR group (n=101, 59.1±16.8 years, 72 males). During 66.5±37 months of clinical follow-up, major adverse cardiac events (MACE) occurred in 89 patients: 85 HF rehospitalizations, 4 deaths, no MI. The number of MACE were significantly higher in the no DFR group than in the DFR group (61.6% vs. 32.4%, P<0.001). Predischarge systolic functional recovery was not a predictor of MACE, but impaired DFR was an independent predictor of MACE (RR=2.952, P=0.010, confidence interval, 1.878–6.955).

Conclusions: Impaired predischarge DFR, regardless of the type of HF or predischarge systolic functional recovery, is an independent predictor of future MACE in HHF. Changes in diastolic function should be carefully monitored and would be useful in risk stratification of HHF.

Key Words: Diastolic dysfunction; Heart failure; Hypertension; Outcomes

Hypertension (HT) is a common health problem and a major risk factor for cardiovascular (CV) diseases or events. Uncontrolled and prolonged elevation of blood pressure (BP) may result in structural and functional changes in the CV system. Hypertensive heart disease (HHD) refers to a constellation of structural and functional abnormalities of the heart associated with hypertension, and HHD includes left ventricular (LV) hypertrophy, as well as systolic and diastolic dysfunction with or without symptoms of heart failure (HF).1

As in life expectancy increases and survival from various CV diseases improves through the advances in medical treatment, the prevalence of HF is gradually increasing worldwide. HT increases the risk of HF by 2–3-fold and probably accounts for approximately 25% of all cases of HF.2,3 Various factors may be involved in the progression from HT to HF, and these include direct insult to cardiomyocytes, alterations in loading conditions, changes in the neurohormonal milieu, development of myocardial infarction (MI), etc.1 Despite the dramatic improvement in HF survival, HF-related rehospitalization is still high.4,5 Previous studies have shown that more than 50% of patients had to be rehospitalized because of HF aggravation within 6 months after discharge from the index HF.6,7

Diastolic dysfunction with or without systolic dysfunction is an important pathophysiologic mechanism of hypertensive HF (HHF),8 and diastolic dysfunction is also an independent predictor of poor clinical outcomes in patients with HF.9 Recent studies, furthermore, have demonstrated that worsening diastolic dysfunction is an independent predictor of death in HF patients with normal ejection fraction (EF),10 and diastolic functional recovery (DFR) at 6 months after index HF is associated with favorable outcomes in patients with acute non-ischemic
cardiomyopathy regardless of LV systolic functional recovery.\(^\text{11}\) However, the effects of predischarge DFR on clinical outcomes in patients with HHF have been poorly studied. The aim of the present study, therefore, was to investigate the effect of DFR on predischarge echocardiography on future clinical outcomes in the patients with HHF.

**Methods**

**Study Design and Population**

The present study was a single-center, retrospective, observational study, and the study protocol was approved by the institutional Review Board (No. 2010-05-092).

From January 2010 to December 2014, a total of 321 patients hospitalized with HHF were identified. After excluding 146 patients, the 175 patients who had both baseline and predischarge echocardiography were divided into 2 groups according to the change in diastolic function on predischarge echocardiography in comparison with baseline echocardiography: DFR group (n=74, 54.2±17.1 years, 55 males) vs. no DFR group (n=101, 59.1±16.8 years, 72 males). The reasons for exclusion were as follows: (1) no baseline or predischarge echocardiography (n=91), (2) lost to clinical follow-up (n=28), (3) other identifiable causes of HF including ischemic heart disease, significant valvular heart disease, cardiomyopathy, or arrhythmia (n=12), (4) previous history of HF or HF-related admission (n=10), and (5) miscellaneous (n=5).

**Study Definitions**

In the present study, HHF was diagnosed by the combination of the following abnormalities:\(^\text{1}\) (1) typical symptoms and/or signs of HF with elevated concentrations of natriuretic peptides, (2) structural heart abnormalities including LV hypertrophy, systolic and/or diastolic dysfunction, in the setting of uncontrolled or poorly controlled HT, and (3) no identifiable cause of HF except for HT.

We defined HF with preserved EF (HFP EF) as HHF with LVEF ≥50%, and HF with reduced EF (HFrEF) was defined as HHF with LVEF <50%.

DFR was defined as an improvement in the grading of diastolic function ≥1 on predischarge echocardiography as compared with baseline echocardiography. In HHP patients with reduced EF, systolic functional recovery was defined as LVEF ≥50% or an improvement in LVEF >10% on predischarge echocardiography as compared with baseline echocardiography.

Major adverse cardiac events (MACE) were defined as cardiac death, HF-related rehospitalization, and MI during clinical follow-up.

**Definition of Hypertension, Diabetes, Dyslipidemia, and Acute MI**

Subjects were considered as having HT if their BP was ≥140/≥90mmHg (as per Joint National Committee VII\(^\text{P}\)) or if they were undergoing treatment for HT. The American Diabetes Association criteria\(^\text{12}\) were used to define diabetes (DM). We considered a subject as having DM when the fasting plasma glucose levels were ≥126mg/dL in 2 consecutive assessments or if the patient was on treatment for DM. Dyslipidemia was diagnosed according to the 2004 update of the National Cholesterol Education Program guidelines.\(^\text{13}\) According to these guidelines, high levels of low-density lipoprotein-cholesterol (≥160mg/dL), low levels of high-density lipoprotein-cholesterol (≤40mg/dL), and high triglycerides (≥150mg/dL) were included.\(^\text{14}\) Acute MI was defined according to current guidelines;\(^\text{15}\) namely, detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTnI) with at least 1 value above the 99th percentile upper reference limit and with at least 1 of the following: symptoms of ischemia, new or presumed new significant ST-segment–T wave changes or new left bundle branch block, development of pathological Q waves on ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and identification of an intracoronary thrombus by angiography or autopsy.

**Biochemical Measurements**

Routine laboratory study was performed on admission. Blood samples to assess the serum lipid profile and glucose were obtained on the morning after admission. Serum N-terminal-pro B-type natriuretic peptide (NT-proBNP) level was measured using an electrochemiluminescence sandwich immunoassay method with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The analytic range of the NT-proBNP assay extends from 5 to 35,000pg/mL. High-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetric CRP-Latex (II) high sensitive assay using an Olympus 5431 auto analyzer (Olympus America Inc., Melville, NY, USA).

**Echocardiographic Examination**

Comprehensive echocardiographic examination, including Doppler studies, was performed at the time of admission and discharge. Echocardiographic images were obtained from various windows using commercially available echocardiography equipment system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Digital cine loops were stored for subsequent offline analysis, and all of the data were analyzed by a computerized offline software package (EchoPAC PC 6.0.0, GE Vingmed Ultrasound).

Chamber quantification was performed according to the current recommendations and included the measurement of LV enddiastolic and end-systolic dimensions or volumes, interventricular septal and posterior wall thicknesses, LV mass, left atrial diameter or volume, and LVEF.\(^\text{16}\) Early (E) and late (A) diastolic velocities of the mitral inflow (E wave) were measured by pulsed-wave Doppler from the apical 4-chamber view, with the sample volume located at the tip of the mitral leaflets. Deceleration time (DT) of the E wave was measured as the time between the peak early diastolic velocity and the point at which the steepest deceleration slope was extrapolated to the zero line. Early diastolic (e\(^\text{'}\)), late diastolic (a\(^\text{'}\)), and systolic (s\(^\text{'}\)) velocities of the septal mitral annulus were obtained by tissue Doppler imaging in the apical 4-chamber view. Diastolic function was further classified into 4 grades according to the current guideline: normal, grade 1, grade 2, and grade 3 diastolic dysfunction.\(^\text{17}\) Diastolic dysfunction ≥grade 2 is considered as advanced dysfunction. Right ventricular systolic pressure was measured by the maximal velocity of the TR jet using a modified Bernoulli's equation.

Global longitudinal strain (GLS) of the LV was measured by automated function imaging (AFI) at a frame rate of 65.2±10.5frames/s. After selecting the optimal 2D image, the timing of aortic valve closure was derived from the pulse wave Doppler of the aortic valve, and the 3-point click method in 3 apical planes (apical 4-chamber, 2-chamber, and long-axis view) was used. The LV in each apical view was divided into 3 levels (basal, mid, and apical), and each
level was subdivided into 2 segments (septal and lateral); thus, the LV was divided into 6 segments for each apical plane. Two points placed at the base along the mitral valve annulus and one at the apex triggered the automated process. AFI noninvasively tracked and analyzed GLS based on the 2D speckle-tracking method and displayed the combined results of GLS of the 3 planes in a single bull's eye summary. The mean value of GLS was calculated by dividing the sum of the GLS of each segment by 18.  

Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences, version 18.0 (SPSS-PC, Chicago, ILL, USA). Continuous variables with normal distribution are presented as mean±standard deviation and were compared using Student’s t-test or the Mann-Whitney U test when group distributions were skewed. Categorical variables were compared using the Chi-square test or Fisher’s exact test, where appropriate. Statistical significance between means for different groups was calculated by ANOVA. A regression analysis using Cox proportional hazard model was performed to identify independent predictors of rehospitalization. The variables with P<0.1 on univariate Cox analysis and clinically relevant ones were tested in the model. All statistical tests were 2-tailed and P<0.05 was considered as statistically significant.

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### Table 1. Baseline Clinical Characteristics of Study Patients With First-Diagnosis Hypertensive Heart Failure

|                      | DFR  
|----------------------|------|------|------|
|                      | (n=74) | No DFR  
|                      | (n=101) | P value |
| Age (years)          | 54.1±17.1 | 59.7±16.8 | 0.058 |
| Male (%)             | 55 (74.3) | 72 (71.2) | 0.394 |
| BMI (kg/m²)          | 26.3±4.9 | 26.2±5.2 | 0.974 |
| Previous HT (%)      | 57 (77.0) | 76 (75.2) | 0.465 |
| HT duration (years)  | 4.1±6.1 | 4.8±6.7 | 0.504 |
| HT medication (%)    | 37 (50.0) | 51 (50.5) | 0.272 |
| Diabetes (%)         | 10 (13.5) | 26 (25.7) | 0.035 |
| Smoking (%)          | 13 (17.5) | 18 (18.1) | 0.545 |
| Dyslipidemia (%)     | 25 (33.3) | 25 (25.7) | 0.508 |
| CVA (%)              | 5 (6.8) | 4 (4.0) | 0.312 |
| CKD (%)              | 5 (6.8) | 10 (9.9) | 0.122 |
| SBP (mmHg)           | 149.1±33.0 | 151.3±31.2 | 0.660 |
| DBP (mmHg)           | 92.8±22.0 | 93.7±20.6 | 0.775 |
| HR (beats/min)       | 82.8±14.6 | 84.7±21.5 | 0.505 |
| HFpEF (%)            | 37 (50) | 38 (37.6) | 0.070 |
| HFrEF (%)            | 37 (50) | 63 (62.3) | 0.070 |

Values are expressed as mean±standard deviation. BMI, body mass index; CKD, chronic kidney disease; CVA, cerebrovascular accident; DFR, diastolic functional recovery; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HT, hypertension; SBP, systolic blood pressure.

### Table 2. Laboratory Findings in Study Patients With First-Diagnosis Hypertensive Heart Failure

|                      | DFR  
|----------------------|------|------|------|
|                      | (n=74) | No DFR  
|                      | (n=101) | P value |
| WBC (/mm³)           | 9,205±3,492 | 8,864±3,477 | 0.528 |
| Hb (g/dL)            | 14.1±1.9 | 13.3±2.6 | 0.026 |
| Glucose (g/dL)       | 140.6±48.4 | 145.5±99.9 | 0.851 |
| BUN (mg/dL)          | 20.9±14.7 | 24.0±12.8 | 0.139 |
| Creatinine (mg/dL)   | 1.35±1.4 | 1.78±0.6 | 0.045 |
| Albumin (g/dL)       | 3.9±0.6 | 3.7±0.6 | 0.024 |
| TC (mg/dL)           | 200.4±41.1 | 177.3±45.4 | 0.041 |
| TG (mg/dL)           | 121.5±35.7 | 105.4±32.6 | 0.284 |
| LDL-C (mg/dL)        | 151.6±57.0 | 141.3±59.8 | 0.706 |
| HDL-C (mg/dL)        | 43.3±11.0 | 36.6±9.9 | 0.131 |
| NT-ProBNP (pg/mL)    | 7,792.1±8,843 | 8,974.1±4,104 | 0.645 |
| hsCRP (mg/dL)        | 1.94±3.5 | 1.78±2.9 | 0.745 |
| HbA1c (%)            | 6.5±1.6 | 6.6±1.5 | 0.318 |

Values are expressed as mean±standard deviation. DFR, diastolic functional recovery; Hb, hemoglobin; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proBNP, N-terminal proB-type natriuretic peptide; TC, total cholesterol; TG, triglyceride; WBC, white blood cells.
Results

Baseline Clinical Characteristics

The HHF group comprised 100 patients with HFrEF (57.2%) and 75 patients with HFP EF (42.8%). DFR was noted in 74 patients (42.3%) on predischarge echocardiography. Baseline clinical characteristics of the DFR and no DFR groups are summarized in Table 1. Baseline characteristics were not different between the groups except that diabetes was more prevalent in the no DFR group.

Laboratory Findings

Laboratory findings are summarized in Table 2. The levels of hemoglobin, albumin and total cholesterol were significantly higher in the DFR group, but the level of serum creatinine was significantly lower than in the no DFR group. Other laboratory findings were not different between groups.

Table 3. Baseline and Predischarge Echocardiographic Findings in Study Patients With First-Diagnosis Hypertensive Heart Failure

| Variables                  | Baseline (DFR n=74) | Baseline (no DFR n=101) | P value | Predischarge (DFR n=74) | Predischarge (no DFR n=101) | P value |
|----------------------------|---------------------|-------------------------|---------|-------------------------|-----------------------------|---------|
| LVEDD (mm)                 | 54.2±7.1            | 56.5±7.1                | 0.038   | 54.9±7.5                | 56.9±7.5                    | 0.207   |
| LVESD (mm)                 | 39.2±9.7            | 42.7±9.6                | 0.022   | 41.1±8.5                | 48.5±8.4                    | 0.325   |
| LVEDV (mm³)                | 108.2±54.9          | 139.8±64.9              | 0.282   | 144.7±34.6              | 162.3±73.7                  | 0.780   |
| LVESV (mm³)                | 56.3±29.4           | 90.8±48.5               | 0.647   | 90.4±29.2               | 105.6±60.8                  | 0.771   |
| EF (%)                     | 50.5±15.7           | 45.8±16.9               | 0.077   | 49.8±14.1               | 47.6±13.3                   | 0.423   |
| GLS (%)                    | 0.06±0.2            | 0.05±0.3                | 0.001   | 0.06±0.2               | 0.05±0.3                    | 0.007   |
| IVS (mm)                   | 12.5±2.5            | 12.7±2.5                | 0.584   | 12.6±2.7               | 12.7±2.4                    | 0.748   |
| PW (mm)                    | 12.7±2.6            | 12.7±2.5                | 0.932   | 12.2±2.7               | 12.4±2.1                    | 0.764   |
| LVMi (g/m²)                | 176.6±60.6          | 179.9±48.1              | 0.787   | 163.1±59.6              | 176.8±47.1                  | 0.317   |
| LAD (mm)                   | 43.8±7.7            | 45.8±6.9                | 0.116   | 44.3±6.9               | 46.3±5.6                    | 0.123   |
| LAVI (mL/m²)               | 44.1±9.1            | 51.2±8.9                | 0.044   | 42.1±9.4               | 49.2±7.5                    | 0.042   |
| E (m/s)                    | 0.68±0.26           | 0.85±0.32               | 0.001   | 0.59±0.27              | 0.71±0.25                   | 0.021   |
| DT (ms)                    | 198.3±64.2          | 181.3±72.8              | 0.154   | 217.8±69.8             | 218.9±89.8                  | 0.949   |
| s' (m/s)                   | 0.09±0.02           | 0.05±0.02               | 0.091   | 0.06±0.02             | 0.05±0.02                   | 0.007   |
| E/e'                       | 13.7±5.7            | 19.7±9.3                | <0.001  | 9.1±2.5                | 16.1±4.4                    | <0.001  |

Values are expressed as mean±standard deviation. DT, deceleration time of mitral inflow; E, early diastolic velocity of mitral inflow; e', early diastolic velocity of mitral septal annulus; EF, ejection fraction; GLS, global longitudinal strain; IVS, interventricular septum; LAD, left atrial dimension; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; PW, posterior septum thickness; s', systolic velocity of mitral septal annulus; RVSP, right ventricular systolic pressure.

Table 4. Prescribed Medications in Study Patients With First-Diagnosis Hypertensive Heart Failure

| Medications                  | DFR (n=74)       | No DFR (n=101) | P value |
|------------------------------|------------------|----------------|---------|
| β-blocker (%)                | 50 (67.5)        | 67 (66.3)      | 0.833   |
| ACEI (%)                     | 7 (9.5)          | 11 (10.9)      | 0.519   |
| ARB (%)                      | 44 (59.4)        | 72 (71.3)      | 0.132   |
| CCB (%)                      | 25 (33.8)        | 30 (29.7)      | 0.275   |
| Loop diuretics (%)           | 24 (32.4)        | 41 (40.6)      | 0.229   |
| Spironolactone (%)           | 32 (43.2)        | 43 (42.6)      | 0.433   |
| Statin (%)                   | 25 (33.7)        | 36 (35.6)      | 0.542   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, aldosterone-receptor blocker; CCB, calcium-channel blocker.
Echocardiographic Findings
Baseline and predischarge echocardiographic findings are summarized in Table 3. Baseline LV dimensions and left atrial volume index (HT) were significantly larger in the no DFR group than in the DFR group. E velocity and E/e' were significantly higher, and the grade of diastolic dysfunction was significantly worse in the no DFR group than in the DFR group. Other echocardiographic findings, including LVEF and GLS, were not different between groups.

On the predischarge follow-up echocardiography, E velocity was significantly higher, and e' velocity was significantly lower, in the no DFR group than in the DFR group. The grade of diastolic dysfunction was significantly worse in the no DFR than in the DFR group. Other echocardiographic findings were not different between groups.

Among 100 patients with HFrEF, LVEF was significantly improved on predischarge echocardiography (from 34.5±9.2% to 42.2±10.7%, P<0.001) and systolic functional recovery was noted in 42 patients (42%). However, LVEF was unchanged in 75 patients with HFpEF (from 63.5±9.5% to 63.0±10.4%, P=NS).

Table 5. Predictors of Major Adverse Cardiac Events on Multivariate Analysis

| Predictor                  | RR    | CI               | P value |
|---------------------------|-------|------------------|---------|
| Age                       | 1.031 | 1.011–1.051      | 0.004   |
| DM                        | 1.754 | 0.876–3.698      | 0.053   |
| Hemoglobin                | 0.987 | 0.847–1.147      | 0.857   |
| Creatinine                | 1.371 | 1.026–1.886      | 0.055   |
| Albumin                   | 0.955 | 0.550–1.658      | 0.870   |
| Total cholesterol         | 1.002 | 0.991–1.013      | 0.756   |
| LVEDD                     | 0.962 | 0.921–1.005      | 0.085   |
| LVESD                     | 0.966 | 0.935–0.999      | 0.060   |
| EF                        | 1.014 | 0.993–1.034      | 0.186   |
| Diastolic dysfunction (≥ grade 2) | 1.382 | 0.716–2.666 | 0.335   |
| No DFR                    | 2.952 | 1.878–6.955      | 0.001   |

CI, confidence interval; DFR, diastolic functional recovery; DM, diabetes mellitus; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; RR, relation risk.

Prescribed Medications
Prescribed medications are summarized in Table 4. Medications for HF and hypertension did not differ between groups.

MACE and Predictors
During 66.5±37 months of clinical follow-up, MACE occurred in 89 patients: 4 cardiac deaths (2.3%), 85 rehospitalization (48.5%), and no cases of MI (0.0%). Overall, the incidence of MACE was significantly lower in the DFR group than in the no DFR group (32.4% vs. 61.6%, P<0.001) (Figure 1). In a subgroup analysis, predischarge DFR was associated with a significantly lower incidence of MACE not only in HFpEF (MACEs: 35.1% in DFR vs. 81.0% in no DFR, P<0.001), but also in HFrEF (MACEs: 29.7% in DFR vs. 49.2% in no DFR, P=0.044) (Figure 1).

In the multivariate analysis, age and no DFR on predischarge echocardiography were significant independent predictors of MACE (Table 5). However, no predischarge systolic functional recovery was not a predictor of MACE in patients with HFrEF (RR 1.818, confidence interval (CI) 0.746–4.420, P=0.188).

In the Kaplan-Meier survival analysis, regardless of the type of HF, cumulative MACE-free survival was significantly lower in the no DFR group than in the DFR group (Figure 2). In the subgroup analysis, overall MACE were not different and individual MACE, either cardiac death or rehospitalization, were also not different between HFpEF and HFrEF (Figure 3).

Discussion
In the present study, we investigated the effect of the predischarge DFR on future adverse events in patients with a first diagnosis of HHF, and the results of the present study demonstrated several clinically important findings. Firstly, regardless of the type of HF or predischarge systolic functional recovery, predischarge DFR was an independent predictor of MACE in patients with their first diagnosis of HHF. Secondly, more than half of the patients with first-diagnosis HHF experienced MACE during clinical follow-up, and thus the development of MACE in HHF should be carefully monitored. Thirdly, despite the high incidence of MACE, the mortality rate of first-diagnosis HHF was only 2.3%, and thus it is suggested that HHF may have a good prognosis, in terms of mortality, as compared with HF of other causes.

Despite improvements in the management of HF, HHF-related mortality has still remained unacceptably high at approximately 30–50% and many patients who survive to discharge after a first attack of HF experience rehospitalization for worsening HF. In the present study, more than half of the patients with first-diagnosis HHF also experienced MACE during more than 6 years of clinical follow-up. Despite the high incidence of MACE, interestingly, the mortality rate was only 2.3% and most MACE were attributed to HF rehospitalization after first-diagnosis HHF. The reason for the very low mortality rate in the present study as compared with previous studies is not entirely clear, but there are several possible explanations. First, the present study included a relatively young population with HHF (54 years old) as compared with previous studies, which included HF patients aged at least 70 years old. Because age is one of the most important prognostic factors, the mortality rate in our study might be very low. Second, the present study only included HHF patients with strict inclusion criteria. Because HHF is known to
diastolic dysfunction is the most important pathophysiologic mechanism of HHF, it is assumed that improvement or worsening of diastolic function may significantly influence the prognosis of HHF. Recent studies, furthermore, have shown that worsening diastolic dysfunction is an independent predictor of death in HF with normal EF, and DFR at 6 months after an index HF is associated with favorable outcomes in patients with acute non-ischemic cardiomyopathy regardless of LV systolic functional recovery.

In the present study, we also evaluated the importance of the changes in diastolic function on the prognosis of HHF, and the results demonstrated that predischarge DFR was an independent predictor of MACE in patients hospitalized with newly diagnosed HHF, regardless of the type of HF or systolic functional recovery. The favorable effects of DFR on the prognosis of HF can be explained by the association of DFR with higher cardiac output in patients with HF irrespective of LVEF.

Considering these results, including those from our study, have a better prognosis than HF of other causes, the mortality rate in the present study might be low. Third, selection bias in a retrospective study may also be an explanation. Taken together, the result of this study suggested that HHF may have a good prognosis, in terms of death, as compared with HF of other causes. Nevertheless, the present study’s results also suggested that the development of HF-related rehospitalization should be carefully monitored in patients with HHF during clinical follow-up.

Considering the poor prognosis of HF, early identification of a high-risk group for adverse clinical outcomes would be important for future planning of patient care and monitoring. For these and other reasons, various prognostic markers of death and/or HF hospitalization in HF have been identified and used for calculating prognostic risk scores. Severe LV diastolic dysfunction is also included among these markers of worse prognosis in HF, but the association between changes in LV diastolic function and the prognosis of HF has been poorly evaluated. Because diastolic dysfunction is the most important pathophysiologic mechanism of HHF, it is assumed that improvement or worsening of diastolic function may significantly influence the prognosis of HHF. Recent studies, furthermore, have shown that worsening diastolic dysfunction is an independent predictor of death in HF with normal EF, and DFR at 6 months after an index HF is associated with favorable outcomes in patients with acute non-ischemic cardiomyopathy regardless of LV systolic functional recovery. In the present study, we also evaluated the importance of the changes in diastolic function on the prognosis of HHF, and the results demonstrated that predischarge DFR was an independent predictor of MACE in patients hospitalized with newly diagnosed HHF, regardless of the type of HF or systolic functional recovery. The favorable effects of DFR on the prognosis of HF can be explained by the association of DFR with higher cardiac output in patients with HF irrespective of LVEF.
it is suggested that a change in LV diastolic function is an important prognostic marker not only in the mid- to long-term follow-up period after discharge from an index HF but also in the early period of HF during hospitalization. Therefore, careful serial evaluation of diastolic function would be useful for risk stratification throughout every stage of HHF.

The prognosis of HFpEF is known to be poor and comparable with that of HFrEF, but the prognosis of HHF with preserved EF or reduced EF has been poorly studied. In the present study, therefore, we evaluated long-term MACE of HHF and also compared long-term MACE between HHF with preserved and reduced EF. Overall MACE were not different and individual MACE, either HF rehospitalization or cardiac death, was also not different between HHF with preserved and reduced EF. In the ATTEND registry, however, all-cause death and HF readmission were significantly higher in HHF with preserved EF than in HHF with reduced EF. Moreover, DFR, theoretically the improvement in LV systolic function by control of BP and the effects of neurohormonal blockade by β-blockers or angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers would be possible explanations for the better prognosis for HHF with reduced EF than for HHF with preserved EF. These observations, however, should be clarified by larger, well-controlled, prospective cohort studies.

Study Limitations

There are several potential limitations in this study. Firstly, the present study was a retrospective, observational study with a relatively small number of patients and thus has all limitations of retrospective analysis, including selection bias for study subjects.

Secondly, the duration of HT was not exactly clear in the present study, even though more than 75% of the patients had a previous history of HT. Of course, the duration of HT may influence long-term MACE, but there was no significant difference between the groups in this study. It might be that many people do not know the exact duration of their HT and there is poor insight into HHF.

Thirdly, the present study included first-diagnosis HHF patients with strict inclusion criteria and both baseline and predischarge echocardiography. Because many of the patients with HHF were excluded from this study, the results of this study cannot be generalized. This issue is a major limitation in the interpretation of this study.

Fourthly, baseline conditions, such as age, DM, hemoglobin, creatinine, albumin, and total cholesterol levels, were different between the groups, and thus these differences may have influenced the occurrence of MACE. Despite the differences present in the univariate analysis, some of them were not significant independent factors in the multivariate analysis. No DFR, however, was an independent predictor of MACE in the multivariate analysis, which included all these parameters. Considering the results of the multivariate analysis, the effects of these parameters on no DFR in predicting future MACE seemed to be small.

Conclusions

In spite of its potential limitations, the present study demonstrated that impaired predischarge DFR, regardless of the type of HF or predischarge systolic functional recovery, was an independent predictor of future MACE in HHF patients. Therefore, changes in diastolic function during hospitalization should be carefully monitored in patients with first-diagnosis HHF and would be useful in the risk stratification of HHF.

Funding

This research was supported by a grant (CRI 13904-21) of Chonnam National University Hospital Biomedical Research Institute.

Conflicts of Interest

None declared.

References

1. Drazner MH. The progression of hypertensive heart disease. *Circulation* 2011; 123: 327–334.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560–2572.
3. Yamasaki N, Kitaoka H, Matsumura Y, Furuno T, Nishinaga M, Doi Y. Heart failure in the elderly. *Intern Med* 2003; 42: 383–388.
4. Peacock F, Amin A, Granger CB, Pollack CV Jr, Levy P, Nowak R, et al. Hypertensive heart failure: Patient characteristics, treatment, and outcomes. *Am J Emerg Med* 2011; 29: 855–862.
5. Weir RA, McMurray JJ, Puri M, Solomon SD, Olofsson B, Granger CB, et al. Efficacy and tolerability of adding an angiotensin receptor blocker in patients with heart failure already receiving an angiotensin-converting inhibitor plus aldosterone antagonist, with or without a beta blocker: Findings from the CANSEARTAS in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial. *Eur Heart J* 2010; 31: 157–163.
6. Ross JS, Chen J, Lin Z, Bueno H, Curtis JP, Keenan PS, et al. Recent national trends in readmission rates after heart failure hospitalization. *Circulation* 2010; 12: 97–103.
7. Joynt KE, Jha AK. Who has higher readmission rates for heart failure, and why? Implications for efforts to improve care using financial incentives. *Circ Cardiovasc Qual Outcomes* 2011; 4: 53–59.
8. Slama M, Susic D, Varagic J, Frohlich ED. Diastolic dysfunction in hypertension. *Curr Opin Cardiol* 2008; 23: 360–373.
9. Somaratne JB, Whalley GA, Poppe KK, Gamble GD, Doughty RN. Pseudonormal mitral filling is associated with similarly poor prognosis as restrictive filling in patients with heart failure and coronary heart disease: A systematic review and meta-analysis of prospective studies. *J Am Soc Echocardiogr* 2009; 22: 494–498.
10. Al Firdausi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, et al. Impact of progression of diastolic dysfunction on mortality in patients with normal ejection fraction. *Circulation* 2012; 125: 782–788.
11. Cavalcante JL, Marek J, Sheppard R, Starling RC, Mather PJ, Alexis JD, et al. Diastolic function improvement is associated with favorable outcomes in patients with acute non-Ischaemic cardiomyopathy: Insights from the multicentre IMAC-2 trial. *Eur Heart J Cardiovasc Imaging* 2016; 17: 1027–1035.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; 289: 2560–2572.
13. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Calvin JE, Castelli WP, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227–239.
14. Hatzitouli AI, Athyros VG, Karagiannis A, Savopoulos C, Charalambous C, Kyriakidis G, et al. Implementation of strategy for the management of overt dyslipidemia: The IMPROVE-dyslipidemia study. *Int J Cardiol* 2009; 134: 322–329.
15. Thyegeen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 16: 1381–1398.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quan-
tification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**:233–270.

17. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiography* 2009; **10**:165–193.

18. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: Definition of normal range. *JACC Cardiovasc Imaging* 2009; **2**:80–84.

19. Kajimoto K, Minami Y, Sato N, Kasanuki H; Investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) Registry. Etiology of heart failure and outcomes in patients hospitalized for acute decompensated heart failure with preserved or reduced ejection fraction. *Am J Cardiol* 2016; **118**:1881–1887.

20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**:2129–2200.

21. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: Findings from OPTIMIZE-HF. *Arch Intern Med* 2008; **168**:847–854.

22. Setoguchi S, Stevenson LW. Hospitalizations in patients with heart failure: Who and why. *J Am Coll Cardiol* 2009; **54**:1703–1705.

23. Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, et al. Diastolic dysfunction in heart failure with preserved systolic function: Need for objective evidence: Results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol* 2007; **49**:687–694.

24. Tobushi T, Nakano M, Hosokawa K, Koga H, Yamada A. Improved diastolic function is associated with higher cardiac output in patients with heart failure irrespective of left ventricular ejection fraction. *J Am Heart Assoc* 2017; **6**:1–7.